ENHANCEMENT OF SOLUBILITY OF REPAGLINIDE THROUGH SOLID DISPERSION METHODS

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CERTIFICATE

This is to certify that the dissertation entitled**, "Enhancement of Solubility of Repaglinide Through Solid Dispersion Methods."** was done by **Mrs. R. KAVITHA** in the Department of Pharmaceutics, Madurai Medical College, Madurai – 20, in partial fulfillment of the requirement for the Degree of Master of Pharmacy in Pharmaceutics, is a bonafide work carried out by her, under the guidance and supervision of **Prof. Mr.A.Abdul Hasan Sathali**, **M.Pharm,** Professor and Head, in the Department of Pharmaceutics, during the academic year 2010 – 2011.

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This is to certify that the Dissertation entitled **"ENHANCEMENT OF SOLUBILITY OF REPAGLINIDE THROUGH SOLID DISPERSION METHODS"** submitted by **Mrs. R. Kavitha** in partial fulfillment of the requirement for the degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by her, under my guidance and supervision during the academic year 2010 – 2011 in the Department of Pharmaceutics, Madurai Medical College, Madurai-20.

I wish her success in all his endeavors.

Place: Madurai

Date: **(Prof. Mr.A.Abdul Hasan Sathali)**

DEDICATED TO MY

BE LOVED PARENTS, HUSBAND AND SON

ACKNOWLEDGEMENT

"I humbly dedicate this little piece of work to Almighty"

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CONTENTS

CHAPTER I

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities(NCE) under development these days are intended to be used as solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration.

In some cases, a small modification in the chemical structure of the compound led to a slight change in biological activity, whereas in some other compounds, even a minor modification led to extreme variations. This led to the recognition of the fact that a great deal of knowledge is required for studying the many factors that affect biological and therapeutic activity of the administered drug.

In recent years, however, the number of new products introduced by the Food and Drug administration, and partly because there are not too many new products left to be discovered.

Therefore a large number of manufacturers have shifted, in part, their attention to marketing either old product in new dosage forms (termed, new drug –delivery systems) or in the same dosage form as generic products. It is for this reason, that many multinational companies are involved in the manufacture of generic products at the present time, although, in the past, a generic product was the domain of mainly "generic companies".

Therefore, the availability of a large number of generic products has given further impetus to research in accessing biological availability of the drug from the administered dosage form. With a large number of generic as well as multi-national companies competing for a larger share of the generic product business, it is no wonder that such terms as bioavailability, drug product selection, generic equivalency, therapeutic efficacy, and drug substitution have become common house-hold words.

Bioavailability is defined as the rate and extent of drug absorption. An intravenously administered dose of a drug in a aqueous solution (without any added ingredient such as buffering agents, preservatives, solubilizing agents, etc.) is considered to be completely available to the biological system because the entire drug dose is placed differently into the blood stream.

It is conceivable, however, that a commercial formulation of an intravenous dose may not necessarily be completely available, if added substances in the formulation form a complex, or are absorbed to the drug. The drug from an extravascularly administered dose, on the other hand, may or may not be completely available.

A number of reasons may be responsible for the lack of complete availability of drug from an extravascularly administered dosage form. These include: incomplete absorption of the drug dose, inactivation of part of the administered dose in the biological environment, metabolism of part of the drug dose at the absorption site, or other similar reasons. Since biologic response is a result of an interaction between the drug substance and the functionally important molecules (receptors) in the living system, unavailability of a portion of the administered drug from the dosage form may result in variation in the expected therapeutic response[1].

ABSORPTION OF DRUGS FROM SOLID DOSAGE FORMS:

When a drug is given orally in the form of a tablet, capsule, or suspension, the rate of absorption is often controlled by how rapid the drug dissolves in the fluids at the absorption site. In other words, dissolution rate is often the rate- limiting (slowest) step in the sequence,

Solid dosage form

↓

Solid drug particles

↓

Drug in solution

↓

Drug in systemic circulation

When dissolution is the controlling step in the over all process, absorption is said to be ***dissolution rate limited.*** Whenever a drug is more rapidly absorbed from solution than from a solid dosage form, it is likely that absorption is rate limited by dissolution.

A general relationship describing the dissolution process was first observed by Noyes and Whitney. The Noyes-Whitney equation states that:

$$dc/dt = ks\ (C_s - C)$$

Where,

- dC/dt - dissolution rate,
- k - Constant,
- S - Surface area of the dissolving solid,
- C_s- solubility of the drug or chemical in the solvent, and
- C- Concentration of the material in the solvent at time **t**.

The constant k is equal to D/h, where D is the diffusion coefficient of the dissolving material, and **h** is the thickness of the *diffusion layer*.

The diffusion layer, like the unstirred water layer in the intestine, is a thin, stationary film of solution adjacent to the surface of the solid. The layer saturated with drug; drug concentration in the layer is equivalent to C_s. The term (C_s –C) represents the concentration gradient between the diffusion layer and the bulk solution. If absorption is dissolution rate limited, C is negligible compared to C_s. Under these conditions, the above equation may be written as:

$$dc/dt = DSC_s/h$$

The above equation describes a diffusion-controlled dissolution process. It is envisioned that when the solid is introduced to the dissolution medium, the drug rapidly saturates the diffusion layer. Drug molecules diffuse from the saturated layer to the bulk (the slow step in the dissolution process) but are immediately replaced in the diffusion layer from the solid surface.

This equation is an oversimplified representation of the dynamics of dissolution; nevertheless, it is qualitatively useful and permits a consideration of the effects of certain important factors of dissolution rate[2].

Fundamentally this process is controlled by the relative affinity between the molecules of the solid substance and those of the solvent. The extent to which the dissolution proceeds under a given set of experimental conditions is referred to as the solubility of the solute in the solvent.

The amount of matter that passes into solution so as to establish equilibrium at constant temperature and so produce a saturated solution is known as the solubility.

PREDICTION OF SOLUBILITY[3]:

Probably the most sought after information about solutions in formulation problem is 'what is the best solvent for a given solute. Theoretical prediction of precise solubility is an involved and occasionally unsuccessful operation but, from knowledge of the structure and properties of solute and solvent, you can make an educated guess. This guess is best expressed in subjective terms, such as 'very soluble' or 'sparingly soluble', as prescribed below in Table: 1.

Description	Approximate weight of solvent(g) Necessary to dissolve 1g of solute
Very soluble	< 1
Freely soluble	Between 1and 10
Soluble	Between 10 and 30
Sparingly soluble	Between 30 and 100
Slightly soluble	Between 100 and 1000
Very slightly soluble	Between 1000 and 10,000
Practically insoluble	>10,000

Often (particularly in pre or early formulation) this is all the information that the formulator requires. A more precise value can be obtained later in the development process.

SOLUBILITY[4]

An important physiochemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter systemic circulation and exert a therapeutic effect, it must first be in solution.

Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than the desirable, consideration must be given to improve its solubility.

The methods to accomplish this depend on the chemical nature of the drug and the type of the drug product under consideration. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility[4].

DISSOLUTION

Variations in the biologic activity of a drug substance may be brought about by the rate at which it becomes available to the organism. In many instances, dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption. This is true for drugs administered orally in solid forms such as tablets, capsules, or suspensions, and for those administered intramuscularly.

When the dissolution rate is the rate-limiting step, anything that affects it will also affect absorption. Consequently, dissolution rate can affect the onset, intensity, and duration of response and control the overall bioavailability of the drug from the dosage form.

The dissolution rate of drugs may be increased by decreasing the particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area

BIOAVAILABILITY ENHANCEMENT THROUGH ENHANCEMENT OF DRUG SOLUBILITY OR DISSOLUTION RATE[5]:

There are several ways by which drug solubility or the dissolution rate can be enhanced. Some of widely used methods are as follows,

- Micronization
- Nanonisation
- Supercritical fluid recrystallization
- Spray freezing into liquid(SFL)
- Evaporative precipitation into aqueous solution (EPAS)
- Use of surfactants
- Use of salt forms
- Use of precipitation Inhibitors
- Alteration of pH of the Drug Microenvironment
- Use of Amorphs, Anhydrates, Solvates and Metastable Polymorphs
- Solvent Deposition
- Precipitation
- Selective Adsorption on Insoluble Carriers
- Solid Solutions
- Eutectic Mixtures
- Solid dispersions
- Molecular encapsulation with cyclodextrins.
- Use of solid solutions,
- Use of eutectic mixtures and Use of solid dispersions

In all these cases, the solute is frequently a poor water-soluble drug acting as the **guest** and the solvent is a highly water-soluble compound or polymer acting as a **host** or **carrier.**

A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one phase system, solid solutions are also called as **molecular dispersions** or **mixed crystals**.

Because of reduction in particle size to the molecular level, solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersions. They are generally prepared by fusion method whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. Such systems, prepared by fusion, are often called as melts. e.g. griseofulvin-succinic acid. The griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin.

SOLID DISPERSIONS:

These are generally prepared by solvent or co-precipitation method whereby both the guest solute and the solid carrier solvent are dissolved in a common volatile liquid solvent such as alcohol. The liquid solvent is removed by evaporation under reduced pressure or by freeze-drying which results in amorphous precipitation of guest in a crystalline carrier.

Thus, the basic difference between solid dispersions and solid solutions/eutectics is that the drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter; e.g. amorphous sulphathiazole in crystalline urea.

Other polymers such as PEG and Crospovidone are also employed to prepare solid dispersions of poorly water-soluble drugs such as Nifedipine and Itraconazole.

Preparation of solid dispersions also presents several **limitations-**

- Since the carrier is hydrophilic and the drug is hydrophobic, it is difficult to find a common solvent to dissolve both components.
- The product is often soft, waxy and processes poor compressibility and flowability.
- Physical stability of the solid dispersion.
- Difficulty in preparation of a reproducible product.

CHAPTER II

SOLID DISPERSION -A REVIEW

Introduction[6]

The oral route remains the favorite route of drug administration due to its convenience, good patient compliance and low medicine production costs. Consecutively for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids.

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption. As a result many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans.

Bioavailability of poorly water-soluble hydrophobic drugs [Class II in Biopharmaceutics Classification System] is restricted by their solubility and dissolution rate. The dissolution rate of these drugs can be improved by decreasing particle size, decreasing crystallinity, and increasing the surface area.

Several studies have been carried out to enhance the dissolution rate of drugs by diminishing the particle size, by creating nano- and microparticles. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high-surface-area carrier such as silica. Here, agglomeration of the drug particles is prevented due to the binding of drug to the carrier.

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release pattern of these drugs, it is possible to increase their bioavailability and reduce side effects. Solid dispersions are one of the most successful techniques to progress drug release of poorly soluble drugs.

SOLID DISPERSIONS[7]

First generation solid dispersion

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They renowned that the formulation of eutectic mixtures improves the rate of drug release and, therefore the bioavailability of poorly water soluble drugs. In the same decade, a number of solid dispersions were described using poorly water soluble drugs, such as sulfathiazole and chloramphenicol using urea as high water soluble carrier.

These solid dispersions fashioned faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the major reasons for the experimental improvements in bioavailability. Later, Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by developing solid solutions through molecular dispersions in place of using eutectic mixtures. The observed Improvements were credited to faster carrier dissolution, releasing microcrystals or particles of drug. These solid dispersions, which could be designed as first generation solid dispersions (Figure 1), were equipped using crystalline carriers.

Second generation solid dispersions

In the late sixties it was experimental that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the first-mentioned were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carrier instead of crystalline.

Fully synthetic polymers include povidone (PVP), poly ethylene glycols (PEG) and Poly methacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxyl propyl methylcellulose (HPMC), ethylcellulose or hydroxyl propyl cellulose or starch derivates, like cyclodextrins.

Third generation solid dispersions

Recently, it has been shown that the dissolution pattern can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These include a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are proposed to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization.

HPMC was also associated with poloxamer and poly oxy ethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion. The addition of surfactants in the formulation containing a polymeric carrier may help to avoid precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles.

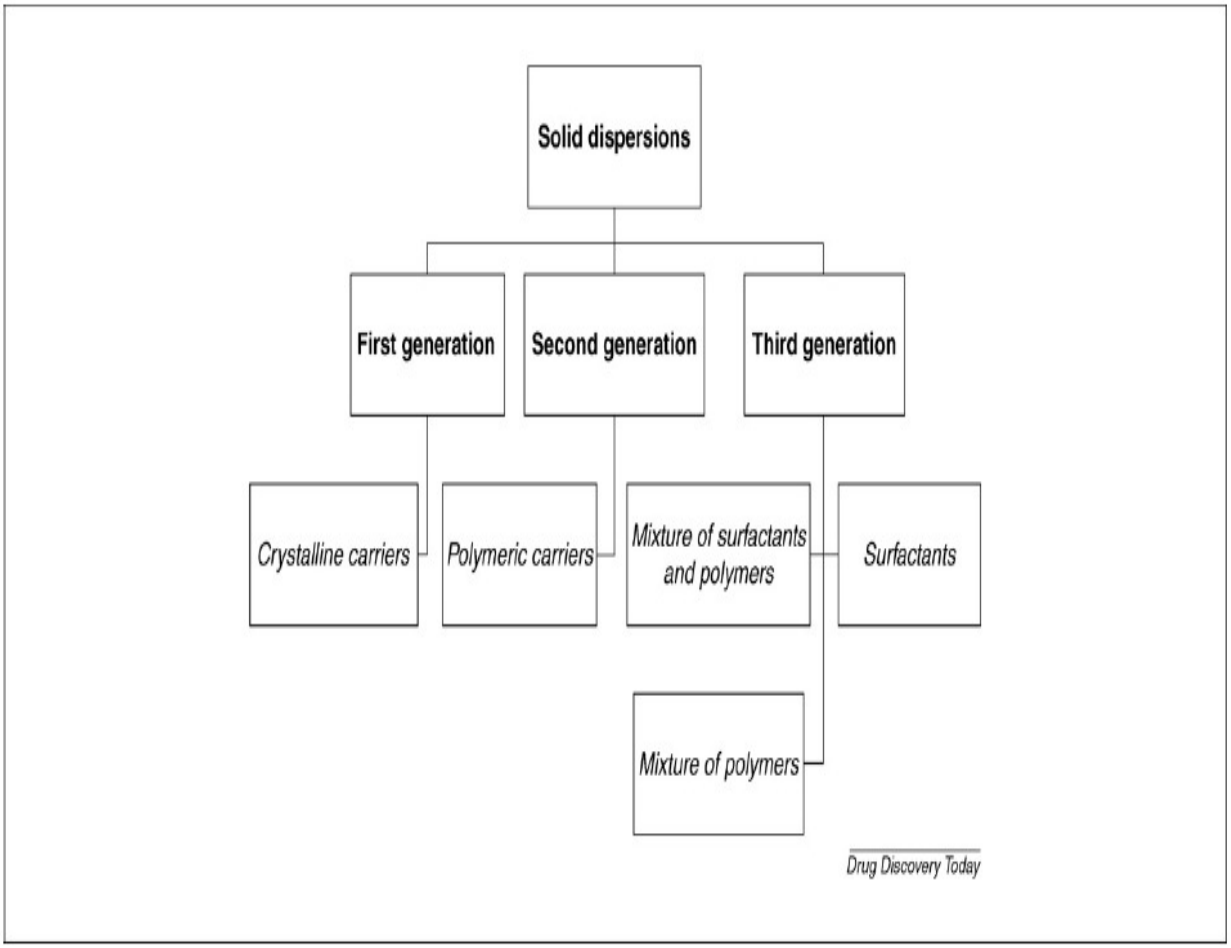


Figure-1: The classification of solid dispersions

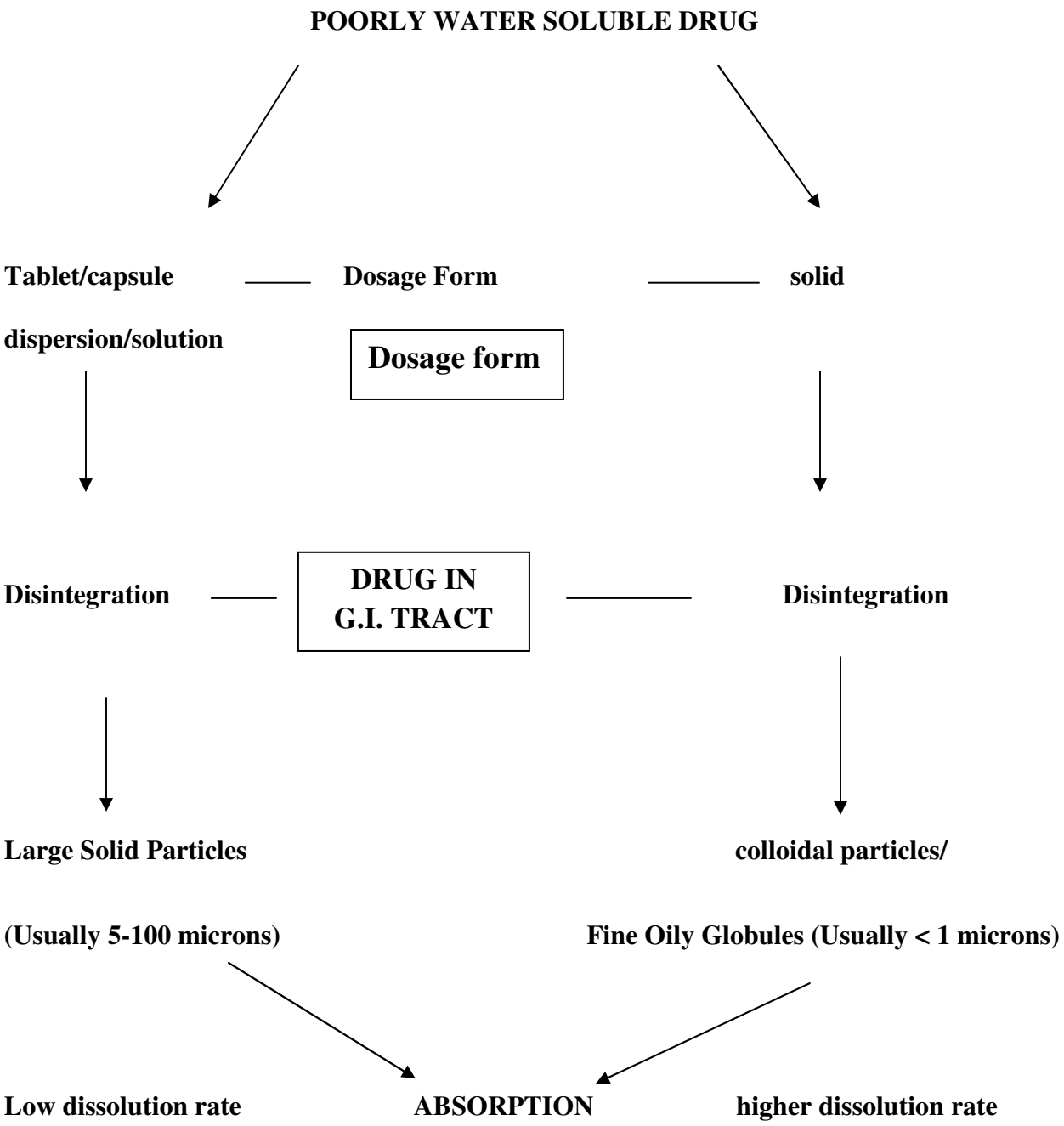


Figure 2 : Schematic representation of the bioavailability enhancement of a poorly water soluble drug by solid dispersion compared with conventional tablet or capsule.

The advantage of solid dispersion, compared with conventional capsules and tablet formulations, is shown schematically in Figure-3 .[8] From conventional capsules and tablets, the in vitro release rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case ,an average particle size of 5 µm is generally the lower limit,although higher particle sizes are preferred for ease of handling , formulation, and manufacturing . On the other hand, if a solid dispersion or a solid solution is used , a portion of the drug dissolves instantaneously to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size[8].

The advantages of solid dispersion system includes,

a. An increase in aqueous solubility of the drug because of its very small particle size.

b. A possible solubilization effect on the drug by the carrier in the surrounding diffusion layer.

c. A reduction or absence of agglomeration of drug particles

d. Excellent wettability and dispersability of the exposed drug paticles in the gastrointestinal fluids.

e. Formation of metastable polymorphic forms

However,solid dispersion does have certain disadvantages which include change in crystallinity and decrease dissolution rate on aging.moisture and temperature have more deterioting effect on these systems and handling is not easy due to tackiness.

PREPARATION TECHNIQUES OF SOLID DISPERSION[9]

A.SOLVENT EVAPORATION METHOD

In this method, physical mixture of two components are dissolved in a common solvent and followed by the evaporation of solvent. This method has been used for a long time in the preparation of solid solution or mixed crystals of organic or inorganic compounds**.**

Advantages of this method:

1. Low temperature requirement for the preparation of dispersion
2. Thermal decomposition of drugs and carriers can be prevented.

Disadvantages of this method:

1. The higher cost of production
2. Incomplete removal of solvent
3. Selection of common solvent

B. MELTING METHOD

The physical mixture of drug and water-soluble carrier was heated to melt and the molten mixture was then cooled and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratios. Decomposition should be avoided due to fusion time and rate of cooling.

C. KNEADING METHOD

The physical mixture of drug an carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1 v/v). The slurry is kneaded for 45

minutes and dried at 450C. The dried mass is pulverized and sieved through sieve no 60 and the fraction was collected.

Advantages of this method:

1. Low temperature requirement for the preparation of dispersion
2. Usage of organic solvent is less**.**

D. MELTING SOLVENT METHOD

It involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. The solvent or drug may not be miscible with the carrier. The liquid solvent used may affect the polymeric form of the rug precipitate in solid dispersion.

Advantages of this method:

1. Low temperature requirement for the preparation of dispersion
2. Usage of organic solvent is less.

E. SPRAY DRYING

Spray drying technique finds more important utility in the pharmaceutical industry due to rapid drying and specific physical characters such as particle size and shape of the product. It is a cost effective process as compared to that of freeze drying resulting in the production of fine solid particles. The operation conditions and design of the drier depends upon the drying characteristics of the product and powder specifications.

F. LYOPHILIZATION TECHNIQUE

This technique was an alternative to solvent evaporation method. Here the drug and carrier are dissolved in common solvent, frozen and sublimed to obtain a lyophilized molecular

dispersion. Lyophilization technique was used to improve the solubility and dissolution rate of many drugs.

G. MELT AGGLOMERATION PROCESS

This technique has been use to prepare solid dispersion where a binder acts as a carrier. The solid dispersion is prepare by heating binder, drug and excipient to a temperature above the melting point or spraying the dispersion of drug in the molten binder on the heated excipient using a high shear mixer. The effect of binder type, method of preparation and particle size are the critical factors influencing the solid dispersion preparation by this method. These parameters results in various dissolution rates, mechanism of agglomerate formation and growth, agglomerate size and distribution.

CHAPTER III

LITERATURE REVIEW

Literature reviews on solid dispersions of a number of drugs have been attempted and reports on them have been well documented.

1. **Heike Bleya et al.,** were prepared solid dispersions by a melting method from the water-insoluble model drugs carbamazepine and nifedipine and polyethylene glycol 1500 (PEG 1500) or 1:1 mixtures of PEG 1500 and the polymers polyvinylpyrrolidone (PVP 30, PVP 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA) and Eudragit EPO (Eudragit),and were characterized by dissolution, powder X-ray diffractometry.
2. **Jani Rupal et al.,** developed Solid dispersions (SDs) of Aceclofenac in PEG-6000, PVP were prepared by solvent evaporation method. The solid dispersion was characterized for physical appearance, solubility and IR. FTIR study reveled that drug was stable in SDs. Solubility of Aceclofenac from SDs increased in distilled water.
3. **Anette Seo et al.,** were prepared solid dispersion by melt agglomeration were agglomerates containing solid dispersions of diazepam as poorly water-soluble model drug in order to evaluate the possibility of improving the dissolution rate. Lactose monohydrate was melt agglomerated with polyethylene glycol (PEG) 3000 or Gelucire® 50/13 (mixture of glycerides and PEG esters of fatty acids). Different drug concentrations, maximum manufacturing temperatures, and cooling rates were investigated. It was established to be possible to increase the dissolution rate of diazepam by melt agglomeration..
4. **Betageri.G.V et al.,** were studied the preparation of solid dispersions and lyophilization of the dispersions designed to enhance the solubility. Solid dispersions of GLY (Glyburide) were prepared using polyethylene glycol 4000 (PEG 4000), PEG 6000 and a mixture of

PEG 4000 and PEG 6000 (1:1 mixture). Dissolution studies showed a significant raise in dissolution of GLY when dispersed in PEGs.

5. **Angela Nedelcu et al.,**were prepared inclusion complexes of repaglinide by using ß-cyclodextrin and ß-cyclodextrin derivatives.dissolution studies showed a significant raise in dissolution of repaglinide when dispersed in ß-cyclodextrin.
6. **Sandrien Janssens et al.,** were designed Kollicoat IR, a new pharmaceutical excipient developed as a coating polymer for instant release tablets, as a carrier in solid dispersions of Itraconazole. The solid dispersions were prepared by hot stage extrusion. DSC and X-ray powder diffraction were used to characterize the miscibility of the drug and the carrier. The results of this study show that Kollicoat IR® is a capable excipient for the formulation of solid dispersions of Itraconazole prepared by hot stage extrusion.
7. **Renata Jachowicz et al.,** were prepared Solid dispersions of different ratios of Gelita collagel as the carrier and lactose were prepared by the spray drying method. In vitro release studies have revealed that by preparing solid dispersions the dissolution rate and the solubility of oxazepam increase obviously, independent of the ratio of drug, carrier and lactose. The properties of the solid dispersions were characterized by X-ray diffraction and polarizing microscopic studies.
8. **Karel Six et al.,** were investigated the performance of three new solid dispersion formulations of itraconazole in human volunteers in comparison with Sporanox®, the marketed form. Solid dispersions were prepared with itraconazole (40%, w/w) and HPMC 2910, Eudragit E100 or a mixture of Eudragit E100-PVPVA64 were manufactured by hot-stage extrusion and filled in gelatin capsules.

9. **Anne Mari Juppo et al.,** were evaluated the formation of solid solution particles in the Solution Enhanced Dispersion by Supercritical fluids (SEDS) process from a model drug and two different types of carriers, mannitol and Eudragit† E100. SEDS was shown to be an effective process for forming intimate blends and solid solutions for the drug and two different types of carriers.
10. **Shailesh V. Biradar et al.,** were developed a solid dispersion of Roxithromycin (ROX), a class IV drug has 50% absolute oral bioavailability due to poor aqueous solubility. Their study dealt with exploring the effect of homogenization, homogenization pursued by freeze drying and homogenization followed by spray drying in the presence of solubilizers on drug solubility and dissolution rate.
11. **Okonogi.S et al.,** were studied to develop the dissolution rate of a sparingly water soluble drug, ofloxacin, by solid dispersion systems with urea and mannitol. DSC, PXRD analysis and IR Spectroscopy were performed to evaluate the physicochemical properties.
12. **Bhaskar Chauhan et al.,** were formulated Solid dispersions (SDs) of glibenclamide (GBM); a poorly water-soluble drug and polyglycolized glycerides (Gelucire®) with the aid of silicon dioxide (Aerosil® 200); as an adsorbent, were prepared by spray drying technique. This study demonstrated the high potential of spray drying technique for obtaining stable free flowing SDs of poorly water-soluble drugs using polyglycolized glycerides carriers with the aid of silicon dioxide as an adsorbent.
13. **Adamo Fini et al.,** were prepared a number of systems at five compositions (5, 10, 20, 30 and 40% w/w) of diclofenac/N-(2-hydroxyethyl) pyrrolidine salt and acidic diclofenac in PEG6000 and Gelucire 50/13, as physical mixtures and as solid dispersions. Powder X-ray diffractograms for the systems examined show shifted and normal peaks, suggesting that the

drug is present inside the samples in different physical states. Drug solubility into the carriers increases with temperature and thermograms show only the melting point peak of the carriers.

14. **Guy Van den Mooter et al.,** were developed solid dispersions made up of itraconazole and Inutec SP1, a new polymeric surfactant, by spray drying and hot-stage extrusion. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) were used to evaluate the miscibility of the components of the dispersions. This study reveals the potential of the new polymeric surfactant as a carrier in the formulation of solid dispersions for poorly soluble drugs.
15. **Naji M. Najib et al.,** worked to provide a valuable insight into the mechanism of dissolution rate enhancement of diflunisal caused by its dispersion in polyethylene glycol (PEG).
16. **Xingwang Zhang et al.,** were studied to characterize lansoprazole (LSP) /PVP solid dispersion prepared by a fluid-bed coating technique. In vitro dissolution test in pH 7.4 phosphate buffer indicated that the dissolution rate was dramatically enhanced even at an LSP/PVP ratio of 1/1.75 or with more PVP. DSC and powder X-ray diffractometry proved the absence of crystallinity in LSP/PVP solid dispersion at a ratio of 1/2 or with more PVP.
17. **Masataka Saito et al.,** were studied to improve the solubility and, physical characteristics of griseofulvin (GF) solid dispersions with saccharides as the dispersion carrier using a roll mixing method. This study suggested that the saccharides with a high molecular weight are useful carriers for solid dispersions.
18. **Huiju Liu et al.,** were designed the dissolution of indomethacin (INM) into polymer excipient Eudragit® E PO (E PO) melt at temperatures lower than the melting point of INM

using a laboratory-size, twin-screw counter rotating batch internal mixer. The outcome showed that the dissolution rate increased with increasing the mixer set temperature, or the screw rotating speed.

19. **Tomoyuki Watanabe et al.,** were studied the states of interaction between indomethacin (IM) and polyvinylpyrrolidone (PVP) in an amorphous solid dispersion prepared by co-grinding were compared with those between IM and silica nanoparticles.
20. **Carina Dahlberg et al.,** were demonstrated the ability of drugs to persuade the wetting of solid dispersion tablets in unexpected ways. Five model drugs of different water solubility and ability to interact with the involved polymers were incorporated in hydrophilic polymer matrices, made of either hydroxypropyl methylcellulose (HPMC) or polyvinyl pyrrolidone (PVP).However, the solid dispersions containing HPMC deviated from this regular behaviour and displayed contact angles below those of the pure compounds involved, either drug or polymer.
21. **Anguiano-Igea.S et al.,** were examined the effect of molecular weight of polyethylene glycols (PEGS) and drug/PEG ratio on the structure and dissolution rates of the solid dispersions with clofibrate. The dissolution rates of clofibrate improved as the molecular weight of PEG increased, but the best results were obtained with PEG 20000.
22. **Yalcin Ozkan et al.,** were examined the release of etodolac from various molecular weight fractions of polyethylene glycol (PEG) solid dispersions. Solid dispersions of etodolac were prepared in different molar ratios of drug:carrier by using solvent and melting methods. The dissolution rate of etodolac is increased in all of the solid dispersion systems compared to that of the pure drug and physical mixtures.

23. **Nattha Kaewnopparat et al.,** were prepared solid dispersions(SD)of curcumin polyvinyl pyrrolidone in the ratio of 1:2, 1:4, 1:5, 1:6, and 1:8 in an attempt to increase the solubility and dissolution. Both solubility and dissolution of curcumin solid dispersions were appreciably greater than those observed for physical mixtures and intact curcumin.
24. **Arvind K. Bansal et al.,** were developed a solid dispersion method for the drug Irbersartan. Irbesartan (IBS) is a hydrophobic drug with poor aqueous solubility and dissolution rate. Solid dispersions of IBS were ready with both small molecules (tartaric acid and mannitol) and polymeric additives (polyvinylpyrrolidone, PVP, and hydroxypropyl methylcellulose, HPMC). Thermal methods were used to evaluate the miscibility of the drug and additives.
25. **Yogesh Pore et al.,** were studied the dissolution behaviour of a poorly water-soluble drug, tadalafil, from its solid dispersion systems with poloxamer 407 has been investigated. Solid dispersion systems of tadalafil were prepared with poloxamer 407 in 1:0.5, 1:1.5 and 1:2.5 ratios using the melting method. Studies established the presence of strong hydrogen bonding interactions, a significant decrease in crystallinity and the possibility of existence of amorphous entities of the drug.
26. **Anette Seo et al.,** were aimed to prepare solid dispersions of diazepam by melt agglomeration as diazepam is a poorly water-soluble model drug so as to evaluate the possibility of improving the dissolution rate. Lactose monohydrate was melt agglomerated with polyethylene glycol (PEG) 3000 or Gelucire® 50/13 (mixture of glycerides and PEG esters of fatty acids) as meltable binders in a high shear mixer. It was found to be feasible to increase the dissolution rate of diazepam by melt agglomeration. A higher dissolution rate was obtained with a lower drug concentration.

27. **Minsuk Lee et al.,** were desired to increase the solubility of sibutramine freebase, the solid dispersion was prepared using a fluid-bed granulator. The solid dispersion containing sibutramine freebase was characterized by DSC and powder X-ray diffraction (XRD). The dissolution rate of sibutramine solid dispersion was considerably increased about 70% than sibutramine freebase.
28. **Punitha.S et al.,** were developed a solid dispersion of celecoxib by Physical triturating method, Solvent evaporation and fusion method were prepared using 1:1, 1:3 and 1:5 ratios of drug and polymer (urea). The prepared dispersion showed marked increase in the saturation solubility and dissolution rate of celecoxib than that of pure drug.
29. **Gopal Venkatesh Shavi et al.,** were formulated solid dispersions of Gliclazide using different water soluble polymers such as polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000) using fusion method and polyvinyl pyrrolidone K- 30 (PVP K 30) by solvent evaporation method. Pharmacokinetic studies of optimized formulation were compared with pure drug and marketed formulation in wistar rats.
30. **Margarit.M.V et al.,** were analyzed the physicochemical characteristics of solid dispersions of pizotifen malate and povidone (Kollidon 12) at different proportions. The results were correlated with findings for physical mixtures with the same proportions.
31. **Biswal.S et al.,** were prepared solid dispersions (SDs) of Gliclazide with polyethylene glycol (PEG) 8000 and compare them with SDs in PEG 6000. Gliclazide SDs containing changeable concentrations of PEG 8000 were ready using the fusion – solvent technique, and their phase solubility behavior and dissolution in 0.1N HCl were assessed at 37^{o}C. The solubility of gliclazide improved with increasing amount of PEG 8000 in aqueous medium.

32. **Patel B.P et al.,** were prepared solid dispersions of Cinnarizine by using PEG 4000, PVP K_{30} exhibited enhanced dissolution rate of Cinnarizine.
33. **Jachowicz.R et al.,** were formulated the ternary solid dispersions of ketoprofen with Macrogol and kollagen hydrolizate derivative as carriers , in which diverse methods of solid dispersion preparation (melting, solvent method, different cooling), different proportions of drug:carriers and molecular weight of Macrogol were tested. The raise in the amount of released ketoprofen from solid dispersion pellets was 3.8-times bigger than from the pellets containing the drug alone.
34. **Hirofumi Takeuchi et al.,** were prepared a Solid dispersion particle of tolbutamide (TBM) by formulating nonporous (Aerosil 200 (hydrophilic), Aerosil R972 (hydrophobic)) or porous (Sylysia 350 (hydrophilic), Sylophobic 200 (hydrophobic)) silica as a carrier and applying the spray-drying (SD) or evaporation (Eva) method.
35. **Nora Anne Urbanetz et al.,** were prepared a solid dispersion of nimodipine by incorporation of a drug in a carrier by melt embedding with in the carrier material. As the dispersivity of the drug is of outstanding importance for its dissolution characteristics, parameters which are supposed to influence crystallinity and dispersivity, It is found that the absence of crystalline drug material in solid dispersions containing nimodipine and polyethylene glycol 2000 is the must for a high dissolution rate and a significant supersaturation in the dissolution medium.
36. **Purvis T. et al.,** were prepared rapidly dissolving Repaglinide powders produced by the Ultra-rapid freezing process.These formulations showed a faster rate of dissolution and show greater bioavailability.

37. **Arias.M.J. et al.,** were demonstrated a solid dispersion technique for triamterene as a method for enhancing the Gl absorption of the drug triamterene has been explored so as to acquire better dissolution characteristics and better bioavailability. In vitro release profiles have been considered and quantified in terms of dissolution efficiency over the first 30 min (DE3,,) and dissolution percentage over the first 30 min (DP,,). The results revealed that there were no significant differences between the three polyethylene glycols (PEGS) under test.

38. **Wei Wu et al.,** were developed the solid dispersions of silymarin (SM) with polyvinylpyrrolidone (PVP) by a one-step fluid-bed coating technique. The process involved the spray application of the ethyl alcohol solution of SM and PVP and subsequent deposition of the coprecipitates onto the non-pareil pellets in drying air flow in a fluid-bed coater. The results demonstrated that the dissolution of PVP/SM solid dispersions was enhanced greatly at PVP/SM ratios of over 4/1. The results indicate that the fluid-bed coating technique has the potential use in the preparation of solid dispersions.

39. **Madhuri Newa et al.,** were developed binary solid dispersion of ibuprofen using poloxamer 188. By melt agglomeration method. And concluded that the solubility, dissolution and absorption rate of ibuprofen were enhanced by preparing ibuprofen solid dispersion with poloxamer 188.

40. **Monica Rao et al.,** were prepared solid dispersion of simvastatin by using PVP K30 and poloxamer 188. It is a concluded to improved bioavailability due to enhancement in rate and extend of drug release.

CHAPTER IV

AIM OF WORK

Repaglinide is a poorly water soluble drug and it belongs to Class II in Biopharmaceutics Classification System and which is prescribed as an anti diabetic drug for the treatment of type II (non-insulin dependent) diabetes mellitus. Solid dispersions of repaglinide would increase the solubility, bioavailability of drug and improve drug efficiency.

Repaglinide is a carbamoyl methyl benzoic acid derivative used as an oral antidiabetic medication in the treatment of type II diabetes, that act primarily by decreasing insulin resistance.

No attempt has been made to increase the solubility of Repaglinide through solid dispersion methods. Hence the dissolution of Repaglinide in citro phosphate buffer $_{P}$H 5 may increase its absorption and finally bioavailability may be enhanced for the conventional dosage formulations.

Therefore the aim of present study is to develop a solid dispersion method for Repaglinide to enhance its solubility. So that the formulation dissolves completely in the citro phosphate buffer $_{P}$H 5 and ensures the complete absorption and bioavailability of Repaglinide.

CHAPTER V

PLAN OF WORK

PART I

1. Determination of λ_{max} for Repaglinide in citro phosphate buffer $_{P}$H 5.
2. Plotting of calibration curve for the drug in citro phosphate buffer $_{P}$H 5.

PART-II

1. Formulation of solid dispersions of Repaglinide using different concentration of carriers by melting method and solvent evaporation method.

PART-III

1. Determination of drug content of all the formulations

PART -IV

1. *Invitro* release studies of the formulated repaglinide solid dispersions by using citro Phosphate buffer $_{P}$H 5 as dissolution medium in USP-type-I method (basket type).

PART-V [11,12,13]

1. IR studies of drug and solid dispersions to determine the interaction between carriers and drug.
2. Differential scanning calorimetry (DSC) studies of selected formulations to determine the status of the drug and carrier.
3. Powder x-ray diffraction (PXRD) studies of selected formulations to determine crystallinity of the drug.

CHAPTER VI

MATERIALS AND EQUIPMENTS

MATERIALS USED

1. Drug-Repaglinide - Gift sample from Dr. Reddy's Laboratories
2. PEG-6000 - S. D. Fine Chemicals
3. Poloxamer 188 - Madras Pharma
4. PVP k_{30} - Nice Chemicals
5. Crospovidone - Nice Chemicals
6. Methanol - Nice Chemicals
7. Disodium hydrogen orthophosphate - Qualigens
8. Citric acid monohydrate - Qualigens

EQUIPMENTS USED

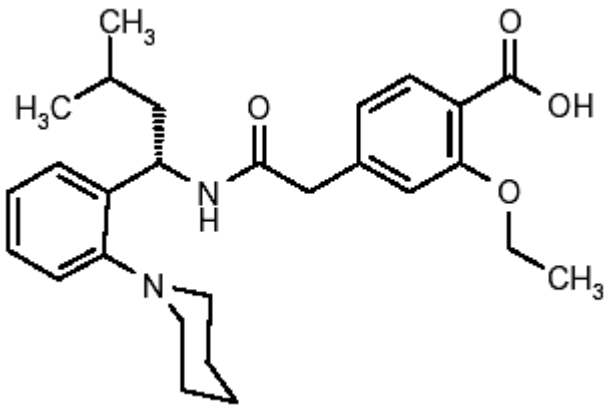
1. Electronic Balance - A&D Company, Japan
2. UV Visible Spectrophotometer - UV Pharma Spec 1700, Shimadzu, Japan
3. Dissolution Apparatus - LABINDIA Disso 2000
4. Water Bath - Mc Dalal & Co
5. Rotary Flask Shaker - SECOR INDIA.
6. Hot Air Oven - SICO

CHAPTER VII

DRUG PROFILE [40,41,42,43]

Repaglinide is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM). This class was developed to specifically control meal-related (prandial) glucose fluctuations in patients with type 2 diabetes mellitus. Like the sulphonylureas, they reduce blood glucose by stimulating insulin secretion. Repaglinide was approved by FDA in 1997.

STRUCTURAL FORMULA:



EMPIRICAL FORMULA:

- $C_{27}\ H_{36}\ N_2\ O_4$

CHEMICAL NAME:

- S (+) 2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid.

DESCRIPTION:

- Nature : Repaglinide is a white to off-white powder
- Solubility : 2.94e-03 mg/mL
- Melting point : 130 to 131 ^{0}C
- Molecular weight : 452.6

SOLUBILITY:

- Freely soluble in methanol.
- Soluble in dichloromethane.
- Insoluble in water

CHEMICAL PROPERTIES:

Loss on drying

- Not more than 0.7%

Residue on ignition

- Not more than 0.1%

Heavy metals

- Less than 0.001%

MECHANISM OF ACTION:

Repaglinide acts by stimulating release of insulin from the β cells of the islets of pancreas inhibiting ATP-sensitive K+ channels, thereby activating the Ca++ channels with increase in intracellular calcium to release insulin. However, repaglinide acts on a different binding site than the sulphonylureas. Repaglinide is not effective in the absence of functioning beta-cells. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

PHARMACOKINETICS:

Absorption:

After oral administration, repaglinide is rapidly and completely absorbed from the Gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (Cmax) occur within 1 hour (Tmax). Repaglinide has a plasma half-life of approximately 1 hour. The mean absolute bioavailability ranges from 56% to 63%.When repaglinide was given along with food the mean Tmax was not changed but the mean Cmax and AUC was decreased by 20% and 12% respectively.

Distribution:

The volume of distribution at steady state (Vss) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism:

Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid, the aromatic amine, and the acyl glucuronide. The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to oxidized dicarboxylic acid and the further oxidation to aromatic amine. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion:

Within 96 hours after dosing with ^{14}C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite oxidized dicarboxylic acid accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

INDICATIONS AND USAGE:

- Repaglinide is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus.
- Also indicated for combination therapy use with metformin or thiazolidinediones.
- If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral blood glucose-lowering agent or insulin should be considered.

DOSE:

The recommended dose range is 0.5 mg to 4 mg taken with meals. Repaglinide may be dosed preprandially 2, 3, or 4 times a day in response to changes in the patient's meal pattern. The maximum recommended daily dose is 16 mg.

For patients not previously treated or whose glycosylated haemoglobin level (HbA1c) is < 8%, the starting dose should be 0.5 mg with each meal. For patients previously treated with blood glucose-lowering drugs and whose HbA1c is > 8%, the initial dose is 1 or 2 mg with each meal preprandially.

There is no fixed dosage regimen for the management of type 2 diabetes with Repaglinide. The patient's blood glucose should be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels are of value in monitoring the patient's longer term response to therapy.

When transferred from longer half-life sulfonylurea agents to repaglinide, close monitoring may be indicated for up to one week or longer. Patients should then be observed carefully for hypoglycemia due to potential overlapping of drug effects.

ADVERSE EFFECTS:

Common adverse events:

The most common adverse events leading to withdrawal were hyperglycemia, hypoglycemia, and related symptoms.

The incidence cardiovascular events like hypertension, abnormal EKG, myocardial infarction, arrhythmias, and palpitations were ≤ 1%.

The incidence of total serious cardiovascular adverse events, including ischemia, was higher for repaglinide than for sulfonylurea drugs in controlled comparator clinical trials.

Infrequent Adverse Events (<1% of Patients):

Postmarketing experience includes reports of rare adverse events like alopecia, hemolytic anemia, pancreatitis, Stevens - Johnson syndrome, and severe hepatic dysfunction including jaundice and hepatitis.

GI events	:	nausea, diarrhea, constipation, vomiting and dyspepsia.
Musculoskeletal events	:	arthralgia and backpain.
Respiratory events	:	sinusitis, rhinitis, bronchitis.

Drug-Drug interactions:

Repaglinide is metabolized by cytochrome P450 enzymes 2C8 and 3A4. Consequently, repaglinide metabolism may be altered by drugs which influence these cytochrome P450 enzyme systems via induction and inhibition. Caution should therefore be used in patients who are on repaglinide and taking inhibitors and/or inducers of CYP2C8 and CYP3A4. The effect may be very significant if both enzymes are inhibited at the same time resulting in a substantial increase in repaglinide plasma concentrations. Drugs that are known to inhibit CYP3A4 include antifungal agents like ketoconazole, itraconazole, and antibacterial agents like erythromycin. Drugs that are known to inhibit CYP2C8 include agents like trimethoprim, gemfibrozil and montelukast. Drugs that induce the CYP3A4 and/or 2C8 enzyme systems include rifampin, barbiturates, and carbamezapine.

Contraindications:

Repaglinide is contraindicated in patients with,

1. Diabetic ketoacidosis, with or without coma.
2. Type1 diabetes.
3. Known hypersensitivity to the drug or its inactive ingredients.

Storage:

- Do not store above 25° C (77° F).Protect from moisture. Keep containers tightly closed.

CHAPTER VIII

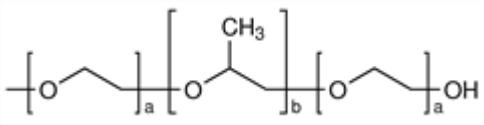
EXCIPIENTS PROFILE

POLOXAMER 188 [44]

SYNONYM

- Lutrol F 68, Pluronic F 68

STRUCTURE



CHEMICAL NAME

- Polyethylene-Polypropylene Glycol

EMPIRICAL FORMULA

- $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$

MOLECULAR WEIGHT

- 8400

FUNCTIONAL CATEGORY

- Emulsifying agent
- Sensitize drug resistant cancers to chemotherapy

DESCRIPTION

- White to off white granules

PROPERTIES

Physical state	:	white powder
Solubility in water	:	soluble in water
Solvent solubility	:	soluble in methanol and chloroform mixture
HLB value	:	29.0

BIOLOGICAL EFFECTS OF POLOXAMER

Originally thought to be inert carrier molecules work led by Kabanov has recently shown that some of these polymers have a very real effect on biological systems independently of the drug they are transporting. The poloxamers have been shown to incorporate into cellular membranes affecting the microviscosity of the membranes.

STABILITY AND STORAGE CONDITIONS

It is stable under ordinary conditions, and should be stored in a well-closed container and protected from light.

SAFETY

It is generally regarded as an essentially non-toxic and non-irritant material at the levels employed as an excipients.

HANDLING PRECAUTIONS

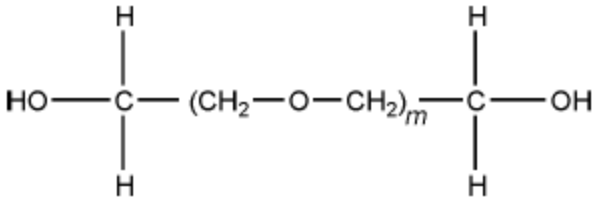
Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk; evaporate the residue under a fume hood. Ground all equipment containing material. Do not breathe dust.

PEG-6000

SYNONYM

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

STRUCTURE



CHEMICAL NAME

- a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

EMPIRICAL FORMULA

- $HOCH_2\ (CH_2OCH_2)mCH_2OH$

Where m represents the average number of oxyethylene groups. Alternatively, the general formula $H(OCH_2CH_2)nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula +1.

MOLECULAR WEIGHT

- 6000

FUNCTIONAL CATEGORY

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

DESCRIPTION

The USPNF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

PROPERTIES

Physical state	:	white flakes
Solubility in water	:	soluble in water
Solvent solubility	:	soluble in methanol,ethanol(95%),dichloromethane, and acetone.

HANDLING PRECAUTION

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended

STABILITY AND STORAGE CONDITIONS

Polyethylene glycols are chemically stable in air and in solution; Polyethylene glycols should be stored in well-closed containers in a cool, dry place.

SAFETY

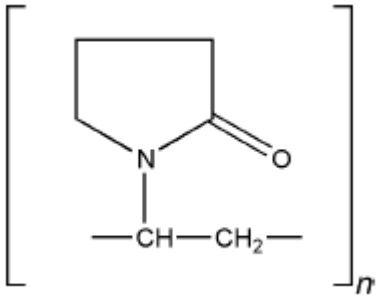
Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials. Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols is relatively low.

PVP K $_{30}$ [44]

SYNONYM

Kollidon, Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; Polyvidone; Polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

STRUCTURE



CHEMICAL NAME

- 1-Ethenyl-2-pyrrolidinone homopolymer

EMPIRICAL FORMULA

- $(C_6H_9NO)_n$ 2500–3 000 000

MOLECULAR WEIGHT

- 50000

FUNCTIONAL CATEGORY

- Disintegrant; dissolution aid; suspending agent; tablet binder

DESCRIPTION

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

PROPERTIES

- Physical state : white powder
- Solubility : freely soluble in acids, chloroform, ethanol (95%), Ketones.
- Ethanol and water : practically insoluble in ether, hydrocarbons, and mineral oil.

HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended

STABILITY AND STORAGE CONDITIONS

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

SAFETY

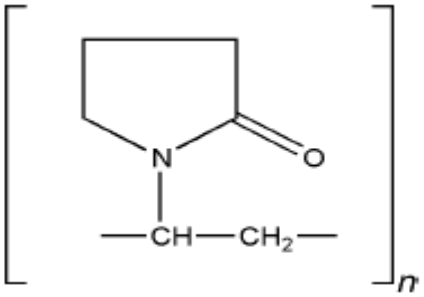
Povidone is widely used as an excipient, particularly in oral tablets and solutions. When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. Additionally it has no irritant effect on the skin and causes no sensitization.

CROSPOVIDONE [44]

SYSNONYM

- Cross linked povidone
- Kollidon CL
- Polyvinyl polypyrrolidone

STRUCTURE



CHEMICAL NAME

- 1-Ethenyl – 2 – Pyrrolidinone homopolymer.

EMPRRICAL FORMULA

- $(C_6 H_9 NO)n$

MOLECULAR WEIGHT

> 1000 000

FUNCTIONAL CATEGORY

- Tablet disintegrant

DESCRIPTION

- White to creamy white powder.

PROPERTIES

- Physical state: White powder
- Solubility in water; insoluble in water
- Solvent solubility: Soluble in methanol and dichloromethane

STABILITY AND STORAGE CONDITIONS

- Crospovidone is hygroscopic; it should be stores in an airtight container in a bol, dry place.

SAFETY

- Crospovidone is use in oral pharmaceutical formulations and is generally regarded as a nontoxic and non irritant material.

HANDLING PRECAUTIONS

- Eye protection, gloves and a dust mask are recommended.

CHAPTER IX

EXPERIMENTAL DETAILS

PREPARATION OF CALIBRATION CURVE FOR REPAGLINIDE

PREPARATION OF DISSOLUTION MEDIUM:[45]

CITROPHOSPHATE BUFFER pH 5:

10.2g of citric acid monohydrate and 18.16g of dibasic sodium phosphate are dissolved in 1L of distilled water.

Preparation of Calibration Curve for REPAGLINIDE:[53]

To a quantity of 100mg of repaglinide, 5ml of methanol is added and the volume is made up to 100ml with methanol. Dilutions are made to get the concentration of 1-10 µg/ml respectively. The solution is scanned in (UV) spectrophotometer and the λ max is found to be 283nm.The absorbance's of the solutions are measured at the λ max .

The calibration graph is drawn by taking the concentration on X axis and respective absorbance in Y axis, to get a straight line as per like Beers law. This standard curve is used to estimate the concentration of the drug release from the formulation during the in vitro dissolution studies.

PREPARATION OF REPAGLINIDE SOLID DISPERSION FORMULATION: [14,15]

Solid dispersions are prepared with the drug repaglinide and polymers (PEG 6000, PVP K_{30}, Poloxamer 188, Crospovidone) using 1:1,1:2, 1:4, and 1:6 weight ratios by means of solvent evaporation and melting methods. Physical mixtures are prepared by mixing manually. The mixtures are passed through a sieve no.120.

Melting method[17,19 ,34,38]:

PEG 6000 is melted in a water bath at 70^0c, the drug repaglinide added in the solid state and the mixture is stirred well until homogeneity would be attained. The mixture allowed to cool slowly at room temperature.

Poloxamer 188 is heated at temp of 55^0c using a thermostatically controlled water bath. Then the drug repaglinide is dispersed in the ratios 1:1, 1:2, 1:4, and 1:6 in the melted carrier poloxamer 188. The resultant mixture is cooled in an ice water mixture and maintained at the cold temp for 2 hrs.

The solidified mass is removed from the ice water mixture and allowed to attain the room temperature (25-30^0c). It is stored at room temperature for 24 hrs, and then pulverized using a glass mortar and pestle. The pulverized mass sifted through a no.120 sieve and then weighed, and transferred to an amber coloured bottle.

Solvent Evaporation Method[26,27,28]:

Repaglinide and PEG 6000, PVP K30, Poloxamer 188, Crospovidone are taken in the ratios of 1:1, 1:2, 1:4, and 1:6 separately. Then the mixtures are triturated and dissolved in methanol. The solutions are evaporated at 40^0 C, the residual mass scraped and sifted through sieve no.120 and kept in desiccator for drying (Table 1).

DRUG CONTENT ANALYSIS

Solid dispersions equivalent to 2mg of Repaglinide are taken and dissolved in minimum quantity of methanol and volume is made up to 50ml. From this solution, aliquot is taken and again diluted with methanol up to 50ml. The solution is assayed for drug content using UV-spectrophotometer method by measuring the absorbance at 283 nm.

INVITRO RELEASE STUDIES [45,51,53,35]:

In-vitro release studies of Repaglinide is performed by using USP type I basket dissolution apparatus in 900 ml of citro phosphate buffer pH 5 maintained at 37° C ± 1° C and 75 rpm. Samples (10 ml) are withdrawn at regular intervals of 5 minutes for 1hr and the same volume of fresh dissolution medium is replaced after every withdrawal. The withdrawn samples are analyzed by U.V. visible spectrophotometer at λ max 283 nm.

The above procedure is performed with repaglinide solid dispersion formulations.

FT-IR STUDIES ;[32,33]

The possibility of drug-excipient interactions are further investigated by FT-IR. The FT-IR graph of pure drug and combination of drug with excipient are recorded .The analysis is performed by using Shimadzu FT-IR Spectrometer. The scanning range is 450-4000 cm^{-1} and the resolution is $4cm^{-1}$. Samples are prepared in KBr pellets.

POWDER X-RAY DIFFRACTION (PXRD) STUDIES; [36,37,39,19]

X- ray diffraction measurements of the solid dispersions are performed on a Rigaku X-ray generator (Japan) with a copper anode (cu Kά radiation, λ = 1.540598 nm, 40 kV), over the 2θ range of $10\text{-}70^0$ to find out the crystalline nature of pure drug and solid dispersed formulations.

SOLUBILITY STUDIES[34,29,30,31]

Excess (usually more than 1mg/ml concentration) of solid dispersion, and physical mixture, pure drug are added to 25ml distilled water taken in stoppered conical flask, vortexed

for 2 minutes and shaken at (Mechanical Shaker) 24 hours. Resultant samples containing undissolved solid dispersions suspended in the test medium are centrifuged at 10,000rpm for 5 minutes and the clear supernatant obtained are filtered (whatman), suitably diluted with distilled water and analyzed spectrophotometrically at 283nm.

DSC STUDIES[18,19]

DSC is performed using Perkin Elmer STA 6000 Thermal Analyzer. The instrument is calibrated with indium standard. Accurately weighed (it varies from 3mg-25mg) samples are placed in an open type ceramic sample pans. Thermo grams are obtained by heating the sample at a constant heating rate of 8ºC/minute. A dry purge of Argon gas (60ml/min) is used for all runs. Samples are heated from 37°C-400°C.

STABILITY STUDY [21,22]

The stability of repaglinide solid dispersion was monitored up to 45 days at ambient temperature and relative humidity (40°C/60%RH). Periodically samples were withdrawn and characterized by dissolution rate measurements.

PREPARATION OF TABLETS[54]:

Of all the formulations, selected solid dispersion (SEM 7) is compressed into tablets. These tablets had a theoretical repaglinide content of 2mg. Lactose is added as tablet diluents. The solid dispersion are blended with talc and magnesium stearate (1% of the total weight of the mixture) and compressed into tablet with a total weight of 200mg. As a reference, tablets from a plain drug (ie. Without any polymer) are made to compare the dissolution behaviour of both the formulations.

CHAPTER X

RESULTS AND DISCUSSION

STANDARD CURVE OF REPAGLINIDE:

The λ max of Repaglinide was determined by scanning the 10µg/ml of the drug solution in citro phosphate buffer solution pH 5. It showed the λ max of 283nm in methanol and citro phosphate buffer solution pH 5.

Linear correlation coefficient was obtained for calibration of Repaglinide. Repaglinide obeys the beer's law within the concentration range of 1 to 10 µg/ml. Calibration plots of Repaglinide in citro phosphate buffer solution pH 5 medium was shown in Figure 3 & Table 2.

FORMULATION OF REPAGLINIDE SOLID DISPERSIONS:[47,48,49]

In the present study, twenty four formulations of Repaglinide were prepared by using water soluble carriers (PEG 6000, Poloxamer 188,Cros povidone, PVP K_{30}) in the ratios of (1:1, 1:2, 1:4, and 1:6) in two methods (Melting Method and Solvent Evaporation Method) with the concentration of the drug being constant (2 mg) (and are shown in Table no: 1). The prepared solid dispersions were found to be uniform and homogenous in appearance.

PEG 6000 and Poloxamer 188 were prepared by both melting method and solvent evaporation methods. Cros povidone, PVP K_{30} were used only in the solvent evaporation method since it is hygroscopic.

DRUG CONTENT

The drug content of the prepared solid dispersion was found to be in the range of (94.45-98.97%) indicating the applications of the present method for the preparation of solid dispersion with high content uniformity (Table: 3).

INVITRO RELEASE STUDIES [45,51,53]

In vitro release profile showed that the formulations MM3, MM7, SEM3, SEM7, SEM11, SEM15, and SEM19 showed faster drug release when compared to other formulations (all prepared with 1:4 ratio). The results indicated that increasing the polymer concentration will increase the dissolution of the drug. Of the selected formulations those prepared with PVP K 30 showed desired release profile when compared to other polymers (PEG 6000, Poloxamer 188 and Cros povidone). Among the formulations SEM7 (PVPK30 1:4) was selected as a best formulations (Table 4 & Figure 5-10).

FTIR STUDIES [49,50,51]

FTIR spectra for pure drug, polymers used and the formulations containing 1:1 ratio of drug and polymers were estimated. Repaglinide pure drug shows the bond vibrations at 3616 cm^{-1} (NH stretching), 3307 cm^{-1} (C-H stretching), 1446 cm^{-1} (O-H stretching), 1334 cm^{-1} (C-H stretching), and 1035 cm^{-1} (C-0 stretching). The bond vibrations of poloxamer shows at 3307 cm^{-1} (C-H stretching) and 1344 cm^{-1} (C-H bending), crospovidone at 3428 cm^{-1} (C-H stretching), 1598 cm^{-1} (C-H bending), PEG 6000 at 3307 cm^{-1} (C-H stretching), 1344 cm^{-1} (C-H bending), and PVP K 30 2933 cm^{-1} (C-H stretching),1566 cm^{-1} (C-H bending).

The results of IR studies revealed that there is no interaction between carrier and drug in the formulations. The results of IR studies are shown in **Figure: 13A-I**

POWDER X-RAY DIFFRACTION (PXRD) STUDIES [53,54]

The X- ray diffraction pattern of Repaglinide exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug, as shown in Figure: 7, but in the formulations no characteristic diffraction peaks were seen for the drug. It was revealed the crystallinity of the drug was highly reduced indicating the drug was converted to its amorphous form (Figure 15).

DIFFERENTIAL SCANNING CALORIMETRY [51,52]

Thermal behavior of pure drug and corresponding drug carrier system are depicted in **Figure 2**. The DSC curve of repaglinide profiles sharp endothermic peak (131.8^0c) corresponding to its melting point, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug was broadened and shifted toward lower temperature, with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of drug in polymer. Moreover, the data also indicate there seems to be no interaction between the drug and polymer (Figure 14).

DRUG SOLUBILITY [50,54]

The equilibrium solubility was determined after 24hours. The solubility of repaglinide in water is known to be 2.94µg/ml at ambient temperature. The physical mixture, formulation were found to have more solubility when compared to pure drug

Form of drug	Solubility (µg/ml) ± SD
Pure drug	2.94 ± 0.11
Physical Mixture	4.86 ± 0.12
Solid dispersion	8.74 ± 0.15

STABILITY STUDY [16,20]

Optimized solid dispersion formulation SEM 7 was subjected to stability studies and there was no significance change in the drug content for 45 days at 40°C and 60% RH. SEM 7 was found to be physicochemically stable and shown best release. (Table No.5)

COMPARISON OF TABLET FORMULATION [54]

The dissolution studies on the solid dispersed tablet and plain tablet were performed in citro-phosphate buffer pH 5 using USP-2(Paddle type).

In vitro release profile of solid dispersion tablets showed a more rapid dissolution of repaglinide than that of plain tablet (Figure 11 & 12).

CHAPTER- XI

SUMMARY AND CONCLUSION

- The purpose of this study was to prepare solid dispersions of Repaglinide to improve the solubility there by enhance the bioavailability.

- Melting Method and Solvent Evaporation Method were employed to prepare solid dispersions.

- The formulated solid dispersions were characterized for in vitro release studies in citro phosphate buffer PH 5.

- The invitro release studies revealed that the increase in the carrier concentration increases the dissolution rate. Faster dissolution rate was observed in the order of

  PVP K_{30} > PEG 6000 > Polaxamer 188 >Crospovidone.

- DSC and FT-IR studies of the all formulations showed that there is no interaction between the drug and the carriers.

- The results of the Powder X-ray diffraction (PXRD) studies proved that crystallinity of repaglinide was remarkably reduced in the best formulation (PVP K_{30} 1:4 ratio).

CONCLUSION:

It is concluded that the melting method and solvent evaporation method, are useful methods for the successful enhancement of solubility of poorly water soluble drug repaglinide with faster dissolution rate. But from the evidence of PXRD studies, the crystallinity of the drug was much reduced in SEM 7 compare to other 6 formulations. Further, it may be assumed that the bioavailability may be increased due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that solid dispersions of repaglinide by using the water soluble carrier PVP K_{30} in the ratio 1:4 prepared by solvent evaporation method provide best drug release (100.2% released in30 mins) among all the selected 6 formulations, and this technique scan be used to enhance the bioavailability of poorly water soluble drugs like repaglinide.

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TABLE: 1

MELTING METHOD

S.NO	NAME OF THE FORMULATION	RATIO OF THE DRUG AND CARRIER	NAME OF THE CARRIER USED
1	MM 1	1 : 1	PEG 6000
2	MM 2	1 : 2	PEG 6000
3	MM 3	1 : 4	PEG 6000
4	MM 4	1 : 6	PEG 6000
5	MM 5	1 : 1	POLOXAMER 188
6	MM 6	1 : 2	POLOXAMER 188
7	MM 7	1 : 4	POLOXAMER 188
8	MM 8	1 : 6	POLOXAMER 188

SOLVENT EVAPOPRATION METHOD

S.NO	NAME OF THE FORMULATION	RATIO OF THE DRUG AND CARRIER	NAME OF THE CARRIER USED
1	SEM 1	1 : 1	PEG 6000
2	SEM 2	1 : 2	PEG 6000
3	SEM 3	1 : 4	PEG 6000
4	SEM 4	1 : 6	PEG 6000
5	SEM 5	1 : 1	PVP K_{30}
6	SEM 6	1 : 2	PVP K_{30}
7	SEM 7	1 : 4	PVP K_{30}
8	SEM 8	1 : 6	PVP K_{30}
9	SEM 9	1 : 1	POLOXAMER 188
10	SEM 10	1 : 2	POLOXAMER 188
11	SEM 11	1 : 4	POLOXAMER 188
12	SEM 12	1 : 6	POLOXAMER 188
13	SEM 13	1 : 1	CROSPOVIDONE
14	SEM 14	1 : 2	CROSPOVIDONE
15	SEM 15	1 : 4	CROSPOVIDONE
16	SEM 16	1 : 6	CROSPOVIDONE

TABLE: 2

CALIBRATION OF REPAGLINIDE

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE±SD*
1	1	0.009 ± 0.000
2	2	0.019± 0.002
3	3	0.029± 0.002
4	4	0.039± 0.001
5	5	0.048± 0.001
6	6	0.059 ± 0.001
7	7	0.069± 0.001
8	8	0.079 ± 0.002
9	9	0.088 ± 0.001

$\gamma = 0.9999$

TABLE: 3

S.NO	FORMULATIONS	DRUG CONTENT±SD*
1	MM 1	98.97 ± 0.355
2	MM 2	96.90 ± 0.355
3	MM 3	95.90 ± 0.355
4	MM 4	94.94 ± 0.941
5	MM 5	97.97 ± 0.410
6	MM 6	96.96± 0.410
7	MM 7	95.97 ± 0.541
8	MM 8	.96.96 ± 0.613
9	SEM 1	95.92 ± 0.410
10	SEM 2	96.91 ± 0.203
11	SEM 3	95.92 ± 0.203
12	SEM 4	94.95 ± 0.203
13	SEM 5	96.94 ± 0.207
14	SEM 6	95.99 ± 0.203
15	SEM 7	96.98 ± 0.207
16	SEM 8	97.92 ± 0.207
17	SEM 9	97.97 ± 0.203
18	SEM 10	97.94 ± 0.207
19	SEM 11	96.93 ± 0.207
20	SEM 12	95.95 ± 0.203
21	SEM 13	94.94 ± 0.201
22	SEM 14	96.95 ± 0.613
23	SEM 15	97.99 ± 0.207
24	SEM 16	95.91 ± 0.410

TABLE: 4A

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*				
	PURE DRUG	MM 1	MM 2	MM 3	MM 4
5	0	13.2 ± 2.12	13.2 ± 2.12	31.2 ± 2.16	19.2 ± 2.12
10	0	17.7 ± 2.09	16.3 ± 0.00	41.9 ± 2.14	29.9 ± 0.04
15	0	25.4 ± 0.00	25.4 ± 0.00	48.1 ± 0.09	34.5 ± 0.00
20	0	30.1 ± 0.04	33.0 ± 2.14	56.0 ± 2.12	46.7 ± 2.12
25	0	36.2 ± 1.90	40.7 ± 2.09	65.3 ± 2.09	59.1 ± 2.20
30	0	45.4 ± 2.12	54.5 ± 2.14	71.7 ± 0.08	66.9 ± 0.00
35	13.2 ± 2.12	48.7 ± 0.04	59.1 ± 1.93	79.5 ± 2.30	74.1 ± 1.83
40	20.8 ± 3.60	58.0 ± 0.00	68.7 ± 2.12	89.1 ± 2.12	87.1 ± 2.02
45	25.5 ± 3.73	68.8 ± 2.14	77.9 ± 2.28	99.8 ± 0.16	90.6 ± 0.09
50	31.6 ± 5.62	76.5 ± 0.04	81.5 ± 0.04	95.9 ± 0.08	95.7 ± 0.21
55	39.3 ± 3.73	83.2 ± 2.09	96.8 ± 2.23	94.9 ± 2.02	100.5 ± 0.16
60	48.5 ± 0.12	91.2 ± 0.04	91.5 ± 0.04	92.6 ± 0.08	96.5 ± 0.16

TABLE: 4B

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	MM 5	MM 6	MM 7	MM 8
5	11.7 ± 0..00	13.2 ± 2.12	11.7 ± 0.00	17.7 ± 2.12
10	16.3 ± 0.00	17.7 ± 2.09	13.3 ± 2.10	25.3 ± 0.04
15	24.8 ± 2.80	25.4 ± 0.00	29.9 ± 0.00	28.5 ± 2.12
20	30.1 ± 0.00	30.1 ± 0.04	39.1 ± 0.00	34.6 ± 0.04
25	36.2 ± 2.12	36.2 ± 1.90	45.3 ± 2.10	43.9 ± 0.04
30	43.9 ± 0.00	45.4 ± 2.12	66.4 ± 0.30	53.2 ± 0.04
35	50.2 ± 2.12	48.7 ± 0.04	71.5 ± 0.00	61.1 ± 2.19
40	58.0 ± 0.00	58.00 ± 0.00	74.8 ± 1.80	67.3 ± 0.00
45	65.9 ± 2.05	68.8 ± 2.14	90.4 ± 0.00	76.5 ± 0.04
50	76.5 ± 0.00	76.5 ± 0.04	92.4 ± 2.10	84.6 ± 2.00
55	81.7 ± 0.00	83.2 ± 2.09	95.9 ± 0.00	88.7 ± 1.8
60	86.6 ± 0.00	91.2 ± 0.04	96.4 ± 0.00	96.1 ± 0.00

TABLE: 4C

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	SEM 1	SEM 2	SEM 3	SEM 4
5	17.7 ± 2.12	26.7 ± 2.16	41.3±2.16	22.2 ±2.12
10	25.3 ± 0.04	28.4 ± 2.12	49.5±2.10	29.9 ± 0.04
15	34.5 ± 3.60	42.1 ± 2.12	60.5 ± 2.26	40.6 ± 2.12
20	45.2 ± 2.16	48.4 ± 0.09	77.0 ±2.28	49.8 ± 2.16
25	54.5 ± 2.12	54.6 ± 2.12	89.7 ± 0.00	54.6 ± 2.16
30	62.5 ±0 .00	59.4 ± 2.12	98.1 ± 0.00	57.9 ± 0.00
35	74.5 ± 2.00	67.4 ± 0.08	100.3 ± 0.00	71.7 ± 0.00
40	87.2 ± 2.12	79.7 ± 2.14	99.8 ± 2.1	88.7 ± 2.14
45	93.6± 2.07	90.0 ± 1.06	99.0 ± 0.1	96.7 ± 2.12
50	95.6 ± 0.00	95.8 ± 2.00	98.1± 0.00	97.2 ± 2.16
55	98.6 ± 0.00	100.3 ± 2.16	97.5 ± 2.02	99.2 ± 2.00
60	99.3 ± 0.28	99.5 ± 0.1	97.0 ± 0.08	99.7± 2.00

TABLE: 4D

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	SEM 5	**SEM 6**	**SEM 7**	**SEM 8**
5	34.3 ± 0.00	44.7 ± 2.12	58.4 ± 2.26	25.2 ± 0.00
10	42 ± 2.12	49.6 ± 2.10	70.6 ± 0.00	43.4 ± 0.00
15	48.2 ± 0.00	62.0 ± 0.00	83.1 ± 2.1	49.6 ± 2.16
20	67.8 ± 2.2	78.7 ± 2.2	94.1 ± 0.00	69.5 ± 2.12
25	70.14 ± 0.00	89.7 ± 0.00	99.7 ± 0.00	89.1 ± 0.49
30	82.4 ± 2.12	97.6 ± 2.00	100.2 ± 1.1	94.4 ± 0.00
35	88.8 ± 2.14	99.2 ± 0.21	99.5 ± 2.30	98.7 ± 0.96
40	99.8 ± 0.00	100.2 ± 2.12	98.7 ± 2.12	100.02 ± 0.00
45	100.9 ± 0.00	99.95 ± 2.28	97.6 ± 0.16	98.5 ± 2.00
50	99.8 ± 0.00	98.50 ± 0.04	95.93 ± 0.08	97.3 ± 0.21
55	96.9 ± 0.00	96.7 ± 0.14	94.97 ± 2.02	96.7 ± 0.16
60	94.4 ± 2.00	95.44 ± 0.04	93.63 ± 0.08	96.59 ± 0.16

TABLE: 4E

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	SEM 9	**SEM 10**	**SEM 11**	**SEM 12**
5	11.7 ± 0.00	16.2 ± 0.00	34.2 ± 0.00	16.2 ± 0.00
10	13.3 ± 2.1	29.8 ± 0.00	43.4 ± 0.00	23.8 ± 2.1
15	29.9 ± 0.00	36.0 ± 2.1	49.7 ± 2.1	25.5 ± 0.00
20	39.1 ± 0.00	46.7 ± 2.1	69.5 ± 2.1	34.6 ± 0.00
25	45.3 ± 2.1	57.5 ± 0.00	71.4 ± 0.00	43.9 ± 0.00
30	66.4 ±0 .3	66.9 ± 0.00	80.9 ± 0.00	53.1 ± 0.00
35	71.5 ± 0.00	71.7 ± 0.00	88.8 ± 2.00	56.4 ± 2.1
40	74.8 ± 1.8	85.7± 0.00	95.1 ± 0.1	77.6 ± 2.2
45	90.4± 0.00	92.8 ± 1.8	100.2 ± 0.1	81.2 ± 0.00
50	92.4 ± 2.1	95.8 ± 0.00	96.1 ± 0.00	86.2 ± 0.00
55	95.9 ± 0.00	100.6 ± 0.14	95.97 ± 2.02	91.2 ± 0.00
60	96.4 ± 0.00	96.6 ± 0.1	94.63 ± 0.08	94.4 ± 1.9

TABLE: 4F

TIME IN MINUTES	CUMULATIVE % DRUG RELEASE±SD*			
	SEM 13	**SEM 14**	**SEM 15**	**SEM 16**
5	11.7 ± 0.00	20.7 ± 0.00	32.7 ± 2.16	17.7 ± 2.12
10	16.3 ± 0.00	29.9 ± 0.00	43.5 ± 0.00	25.3 ± 0.04
15	24.8 ± 2.80	37.5 ± 2.1	48.2 ± 0.08	28.5 ± 2.12
20	30.1 ± 0.00	48.2 ± 0.00	66.5 ± 3.5	34.6 ± 0.00
25	36.2 ± 2.12	54.6 ± 2.12	71.4 ± 0.00	43.9 ± 0.00
30	43.9 ±0 .00	59.4 ± 2.12	80.9 ± 0.00	53.1 ± 0.00
35	50.2 ± 2.12	70.1 ± 2.00	90.3 ± 0.04	61.1 ± 2.19
40	58.0 ± 0.00	76.4± 0.00	93.8 ± 2.1	67.3 ± 0.00
45	65.9± 2.05	81.0 ± 0.04	100.2 ± 0.1	76.5± 0.04
50	76.5 ± 0.00	88.8 ± 2.00	96.1 ± 0.00	84.6 ± 2.00
55	81.7 ± 0.00	91.5 ± 0.14	95.97 ± 2.02	88.7 ± 1.80
60	86.6 ± 0.00	96.5 ± 0.1	94.63 ± 0.08	96.1 ± 0.00

TABLE – 5

STABILITY STUDIES - DRUG CONTENT ESTIMATION

Formulation code	Percentage drug content.				
	0 day	**7th day**	**15th day**	**30th day**	**45th day**
MM3	98.54	97.65	97.47	97.94	97.23
MM7	99.47	98.67	98.71	98.12	97.69
SEM3	98.57	99.47	98.15	98.97	99.12
SEM7	97.25	96.98	98.72	99.10	97.15
SEM11	98.45	98.12	97.69	97.98	98.30
SEM15	96.15	97.18	97.76	98.92	99.65

FIGURE 3

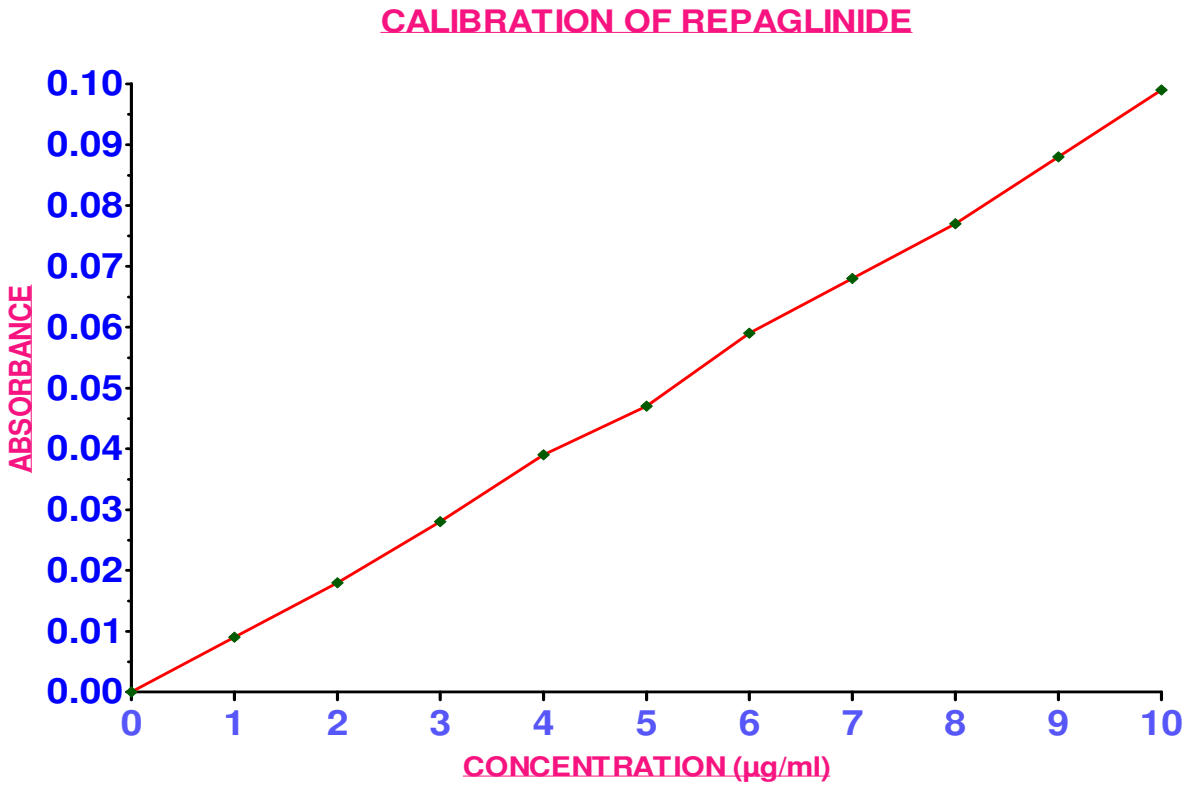

CALIBRATION OF REPAGLINIDE
ABSORBANCE
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
1
2
3
4
5
6
7
8
9
10
CONCENTRATION (µg/ml)

FIGURE-4

UV-ABSORPTION SPECTRUM OF REPAGLINIDE IN CITROPHOSPHATE BUFFER pH5

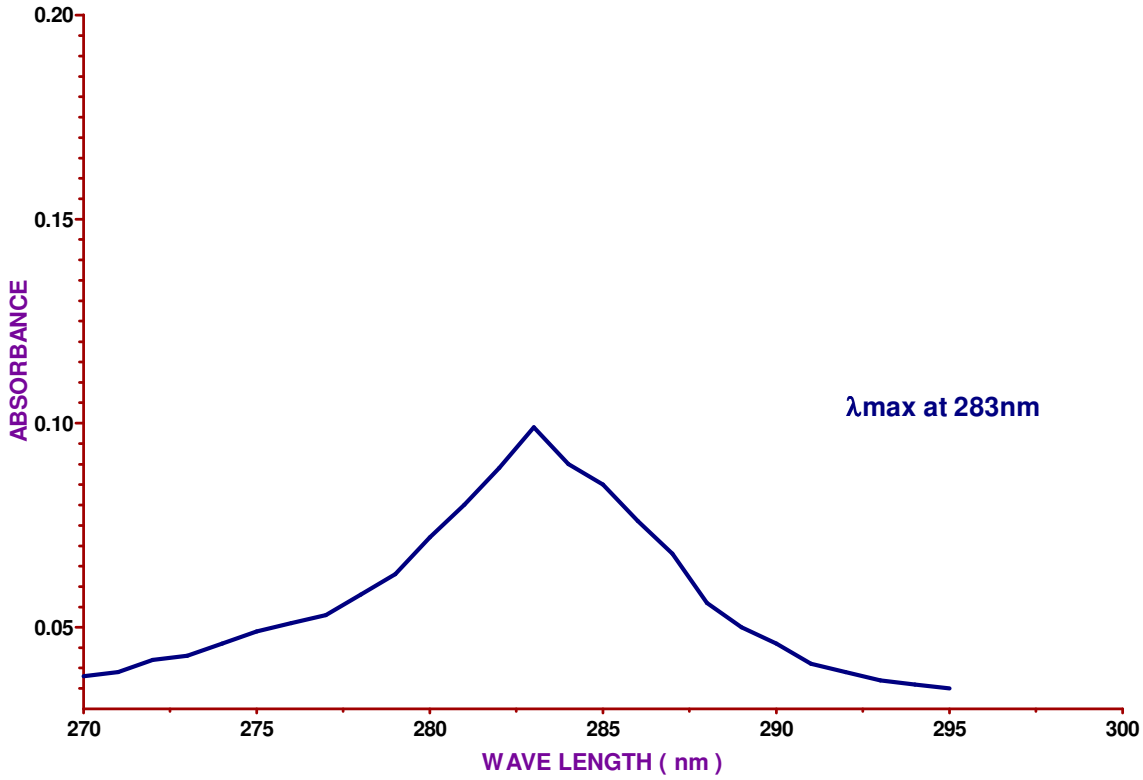


FIGURE 5

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND PEG 6000 BY MELTING METHOD.

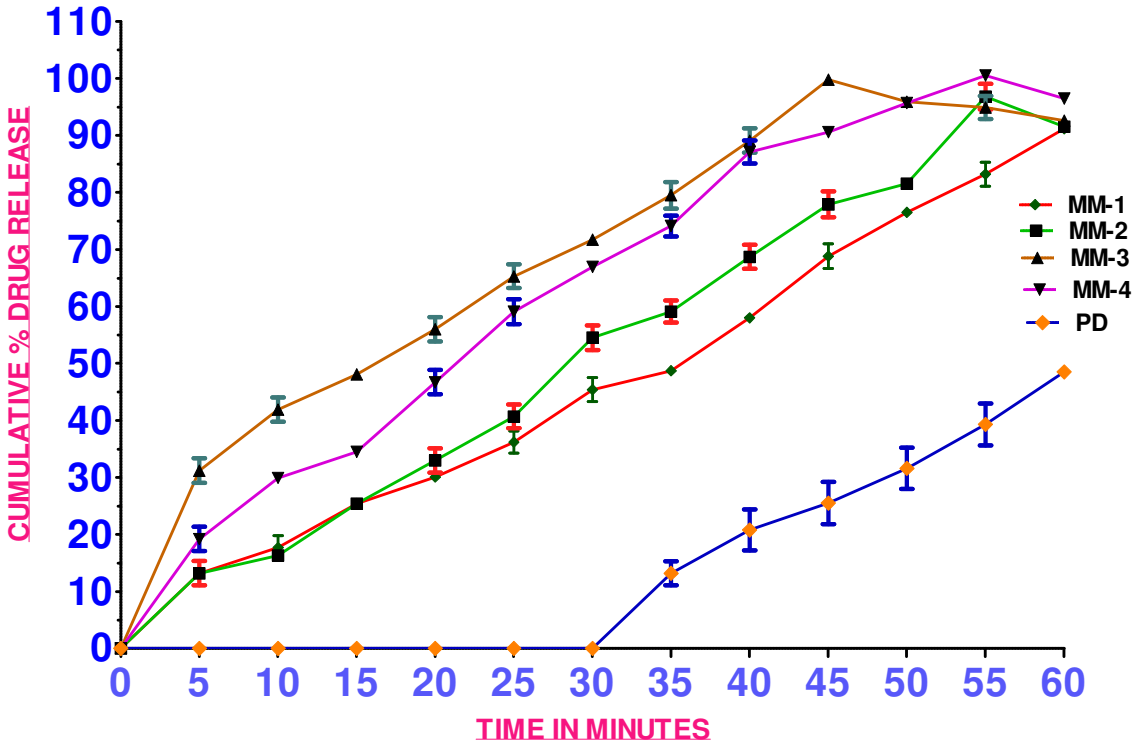


FIGURE 6

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND POLOXAMER 188

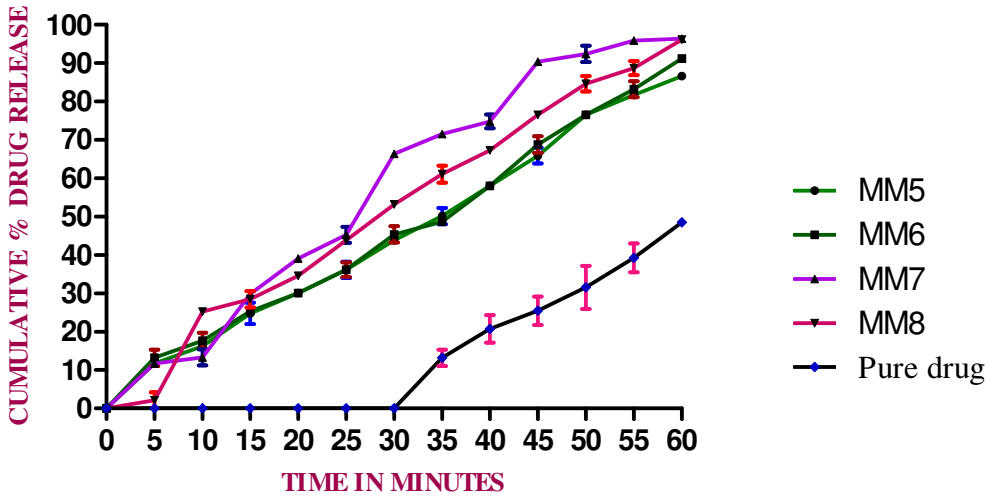


FIGURE 7

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND PEG 6000.

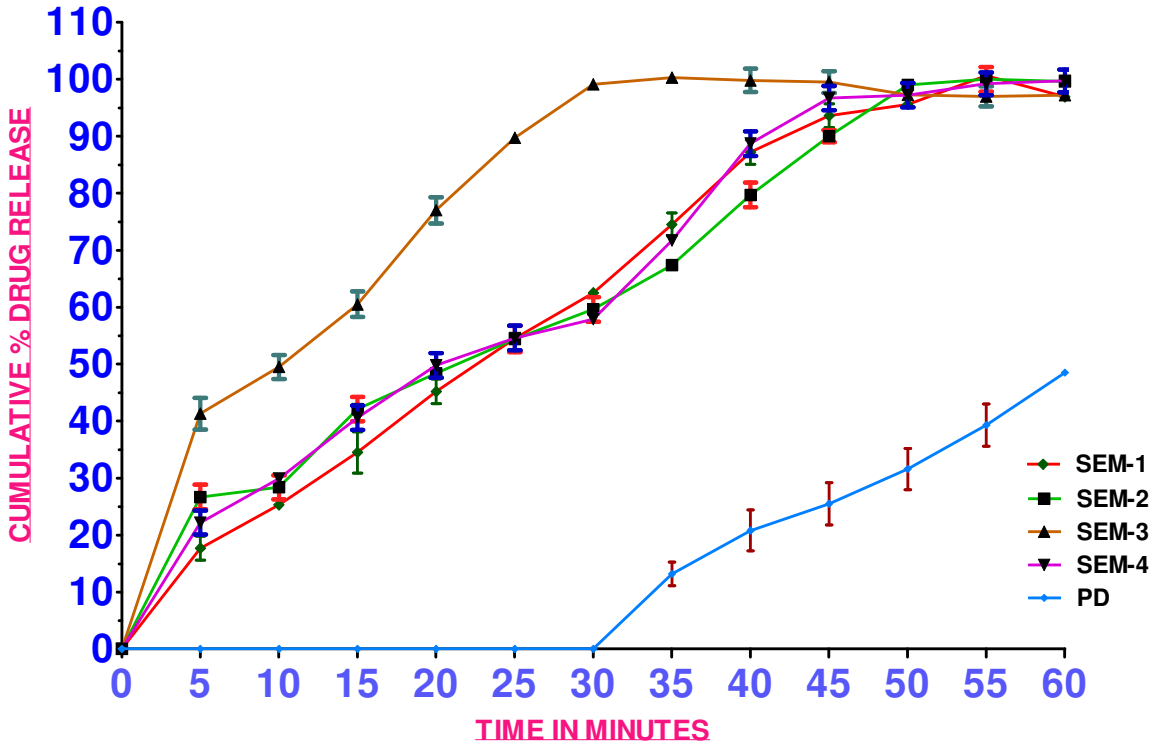


FIGURE 8

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND PVP K30.

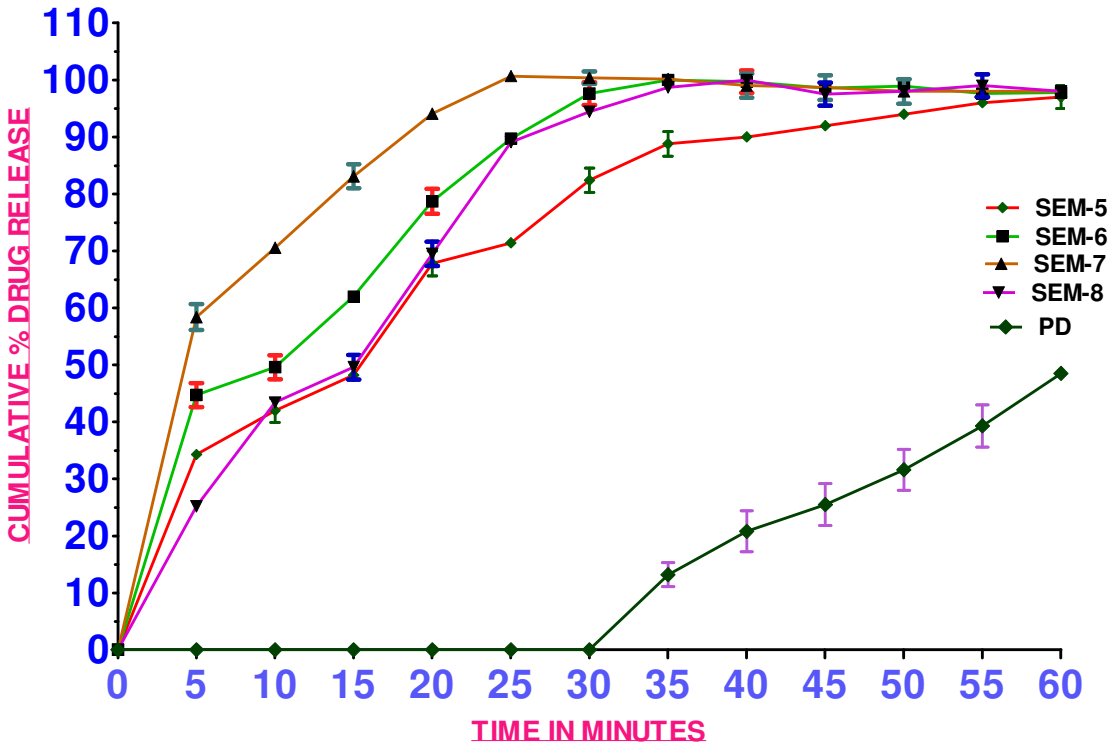


FIGURE 9

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND POLOXAMER188.

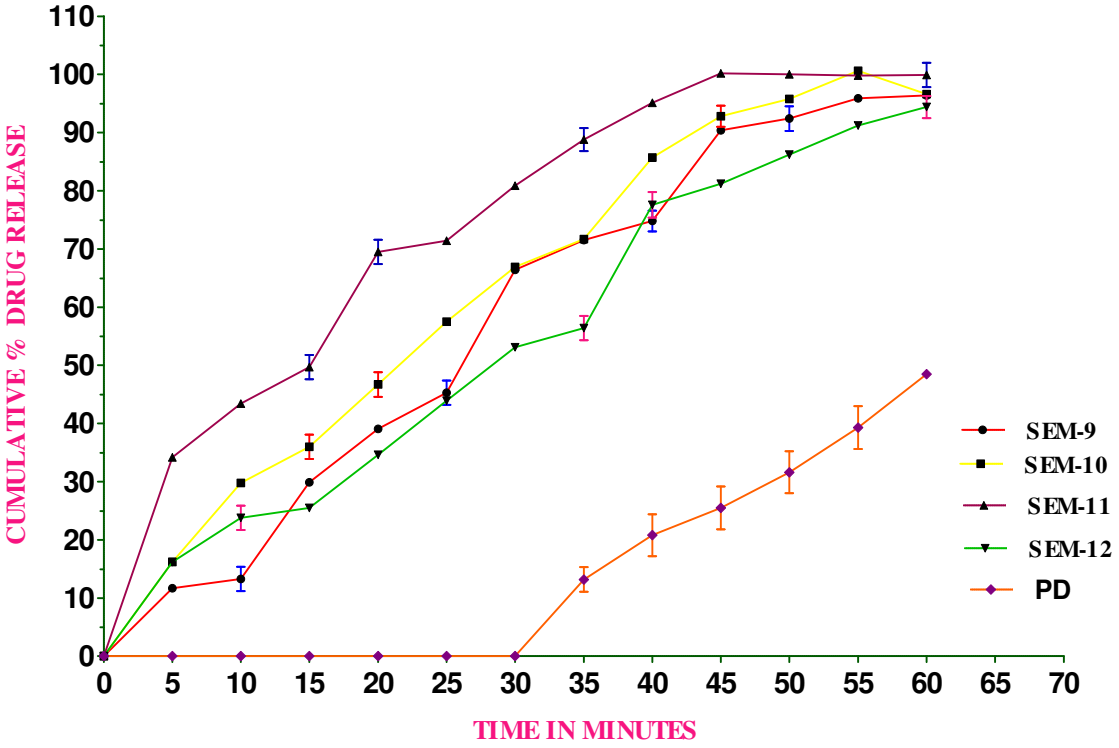


FIGURE 10

COMPARISON OF INVITRO RELEASE PROFILE OF VARIOUS RATIOS OF REPAGLINIDE AND CROSSPOVIDONE.

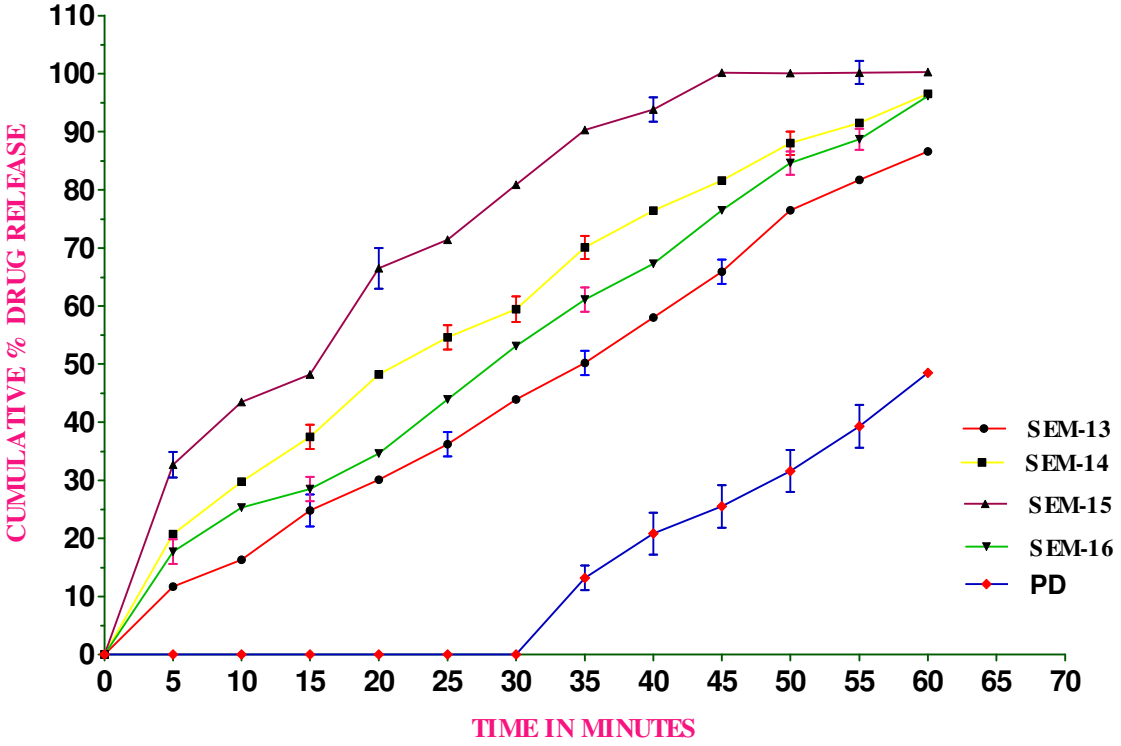


FIGURE 11

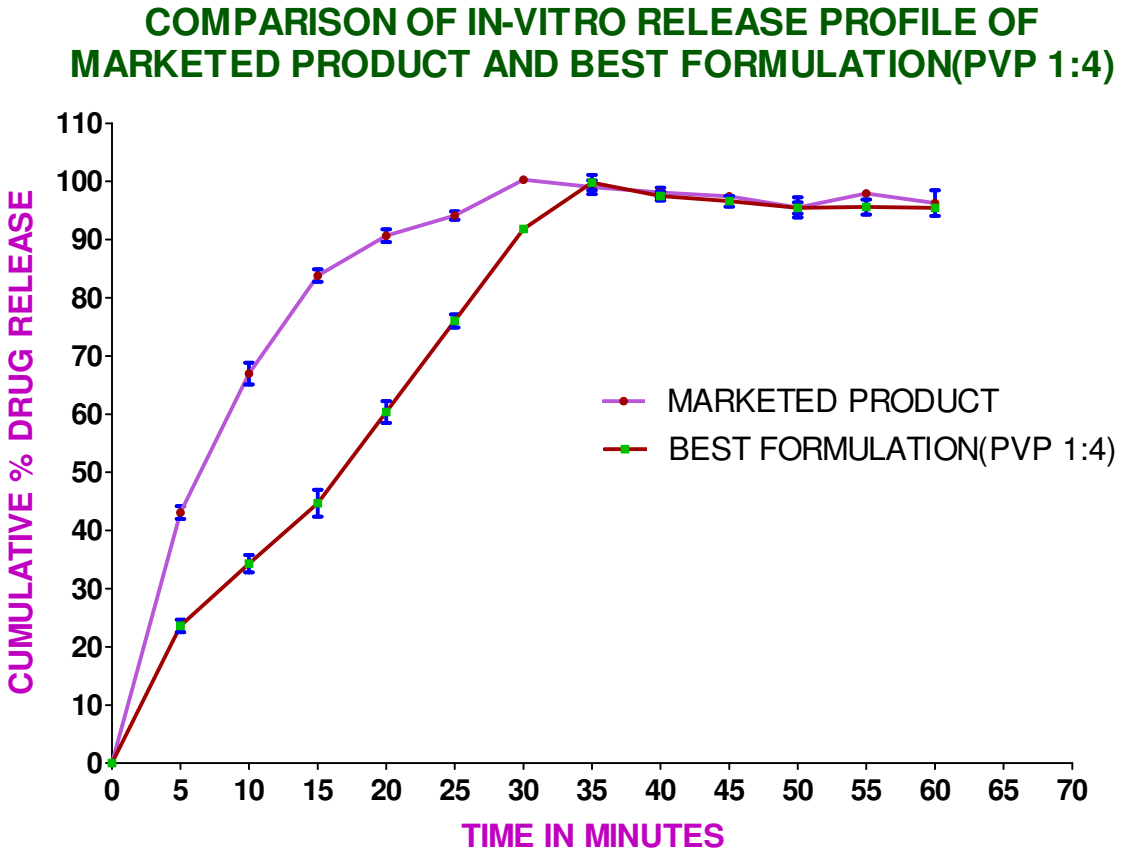

COMPARISON OF IN-VITRO RELEASE PROFILE OF MARKETED PRODUCT AND BEST FORMULATION(PVP 1:4)
CUMULATIVE % DRUG RELEASE
TIME IN MINUTES
MARKETED PRODUCT
BEST FORMULATION(PVP 1:4)
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70

FIGURE 12

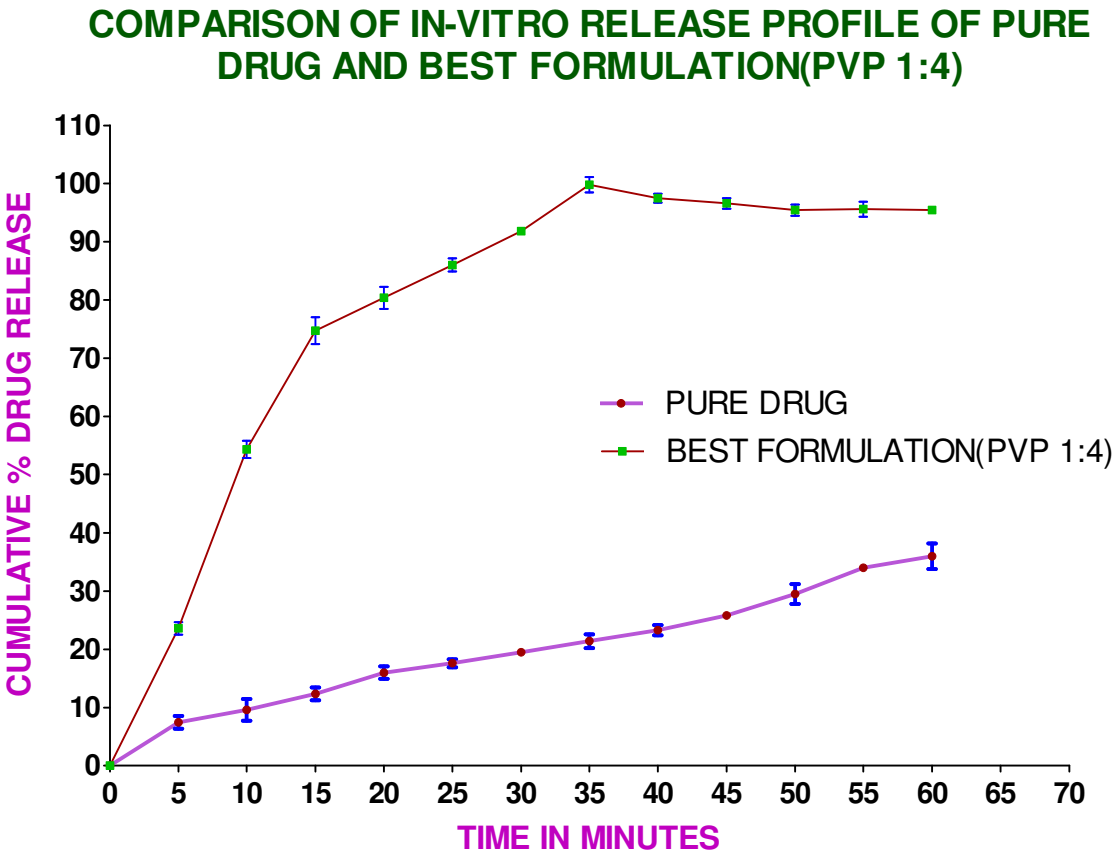
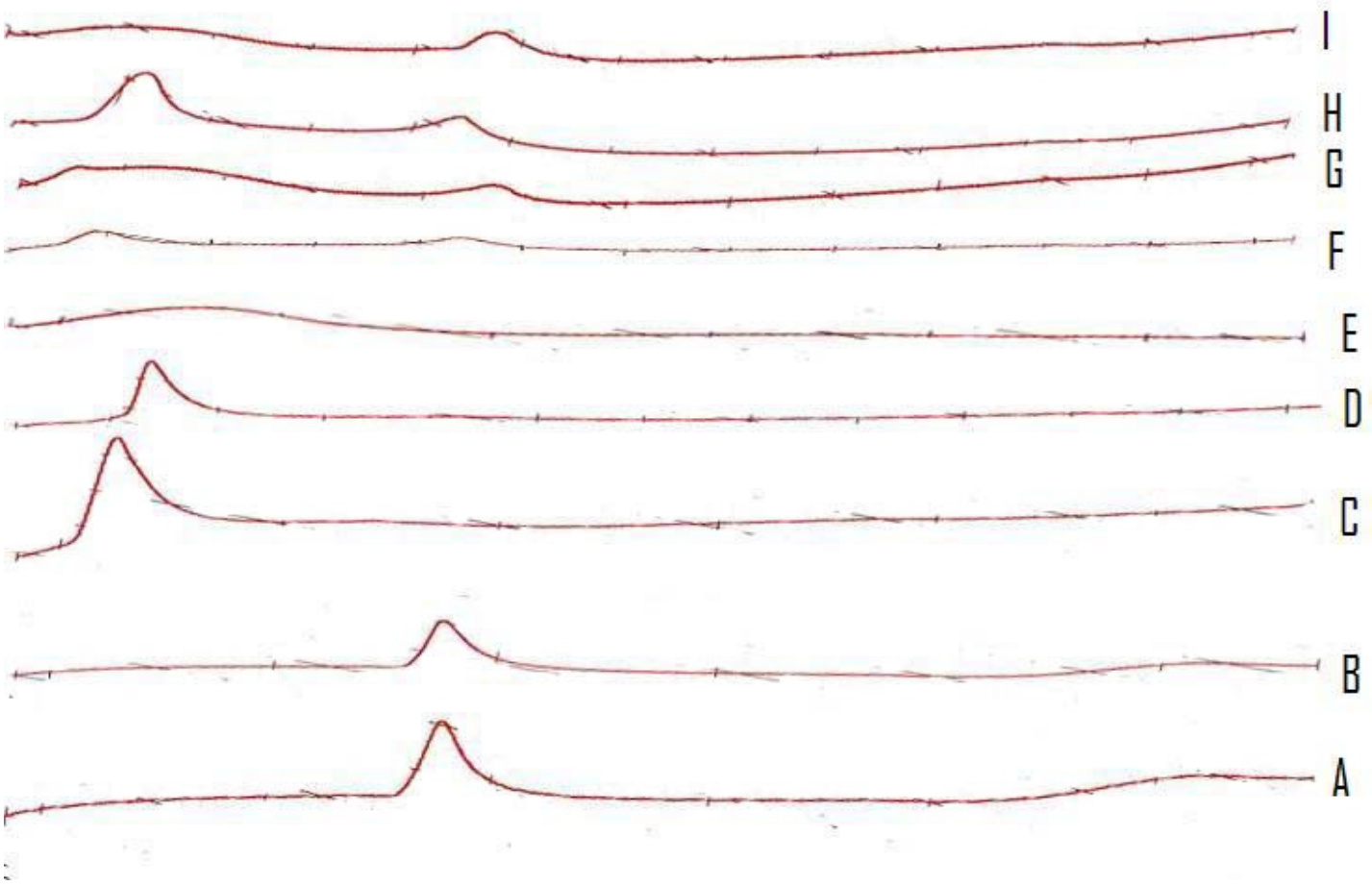

COMPARISON OF IN-VITRO RELEASE PROFILE OF PURE DRUG AND BEST FORMULATION(PVP 1:4)
CUMULATIVE % DRUG RELEASE
TIME IN MINUTES
PURE DRUG
BEST FORMULATION(PVP 1:4)
0
10
20
30
40
50
60
70
80
90
100
110
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70

FIGURE 13

FIGURE 14

DIFFERENTIAL SCANNING CALORIMETRY STUDIES



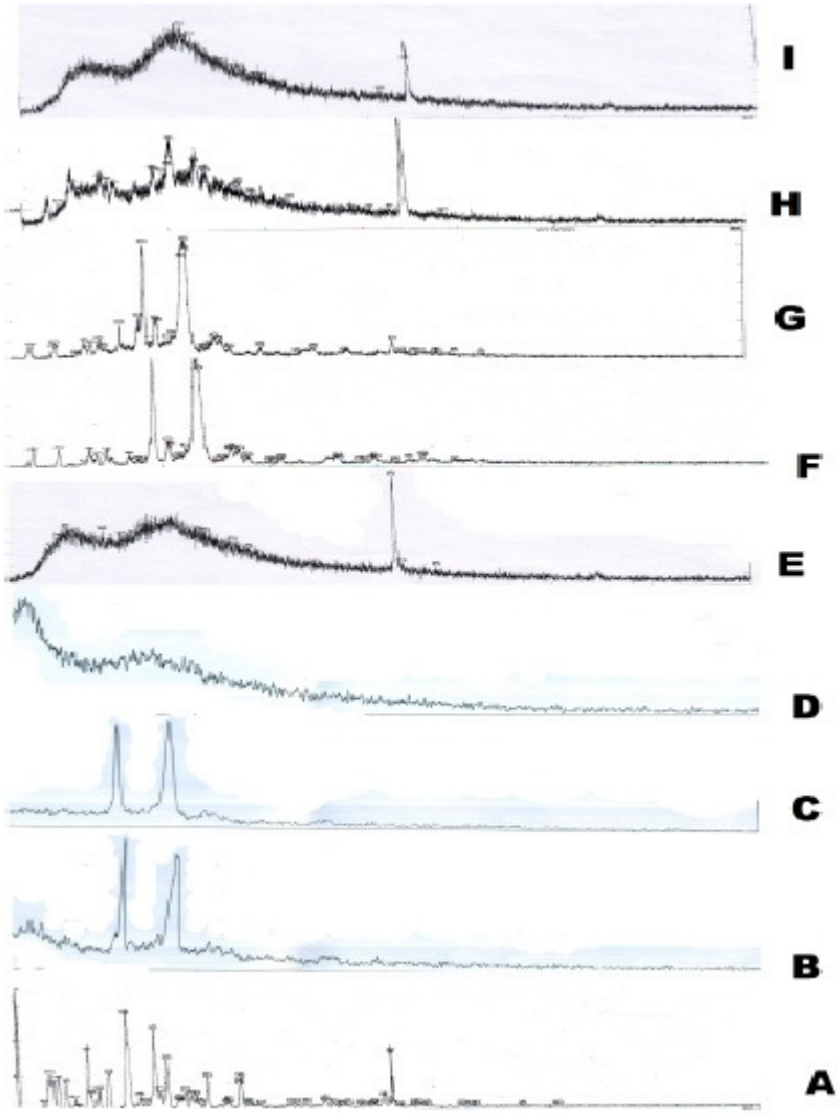
A. PURE DRUG - REPAGLINIDE B. PEG 6000 C. PVP K 30 D. POLOXAMER 188

E. CROSPOVIDONE F. DRUG + PEG 6000 G. DRUG + PVP K30

H. DRUG + POLOXAMER 188 I. DRUG + CROSPOVIDONE

FIGURE 15

X-RAY DIFFRACTION STUDIES

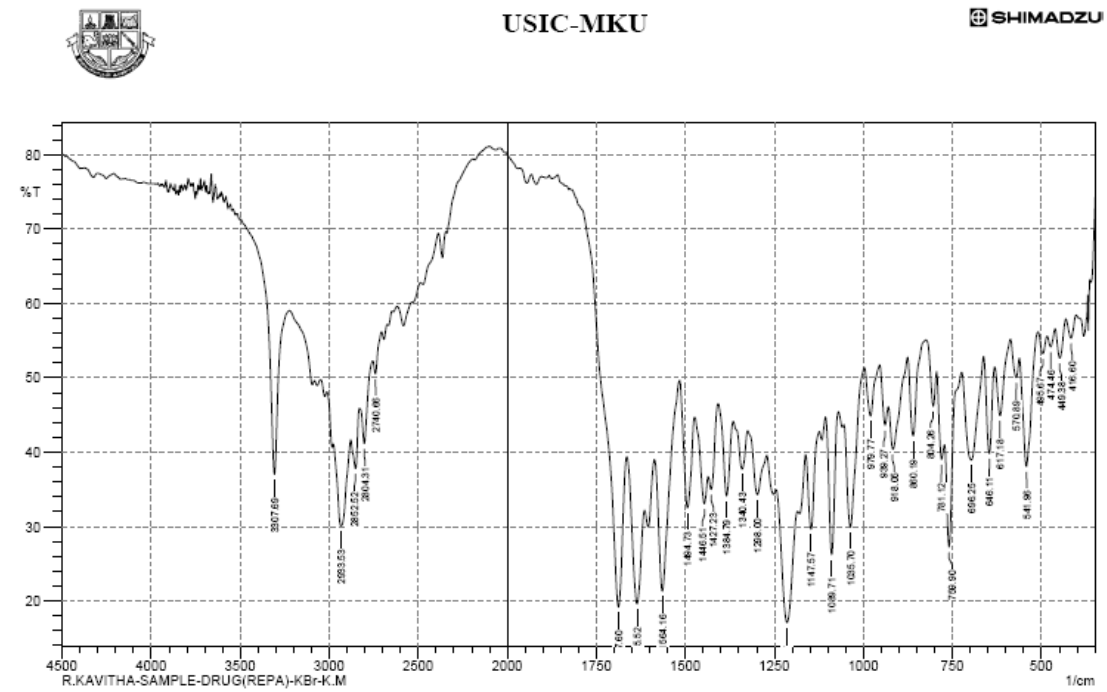


A-REPAGLINIDE B-PEG 6000 C-POLOXAMER 188 D-PVPK30

E-CROSPOVIDONE F-DRUG+PEG 6000 G-DRUG+POLOXAMER

H-DRUG+PVPK30 I-DRUG+CROSPOVIDONE

FIGURE – 13A



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Apodization;

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FIGURE – 13B

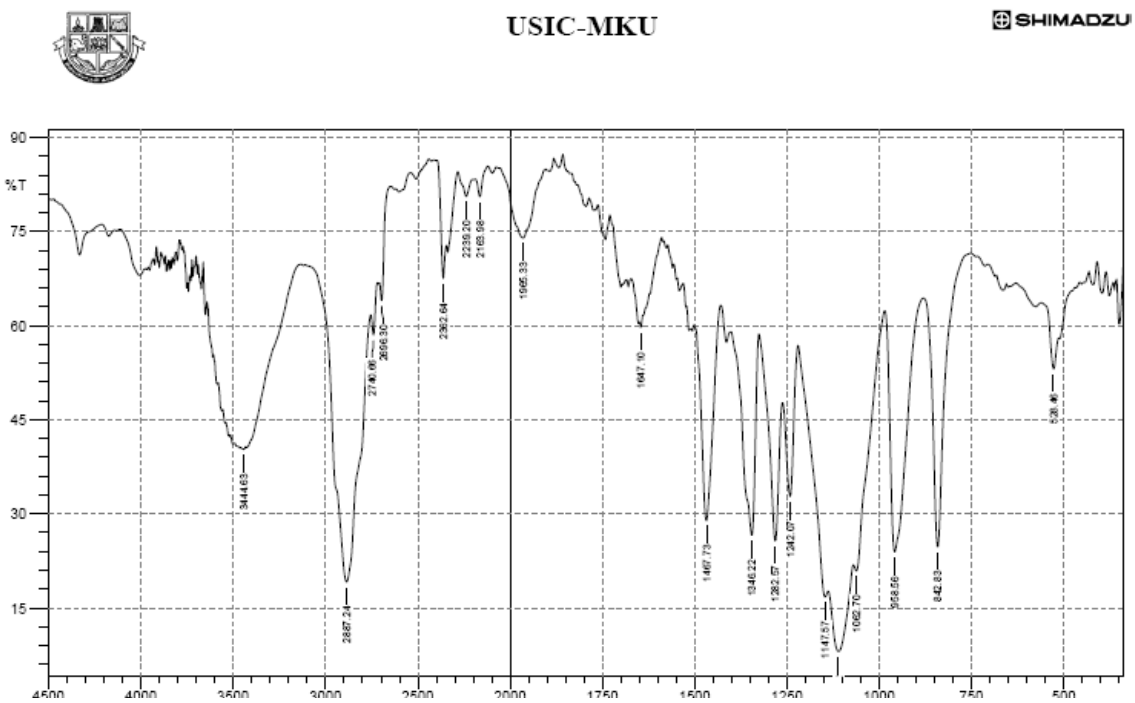
USIC-MKU
SHIMADZU
%T
90
75
60
45
30
15
3444.63
2887.24
2740.06
2696.30
2362.64
2239.20
2183.68
1995.33
1647.10
1467.73
1346.22
1282.07
1242.07
1147.57
1062.70
968.56
842.83
538.47
4500
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500

FIGURE – 13C

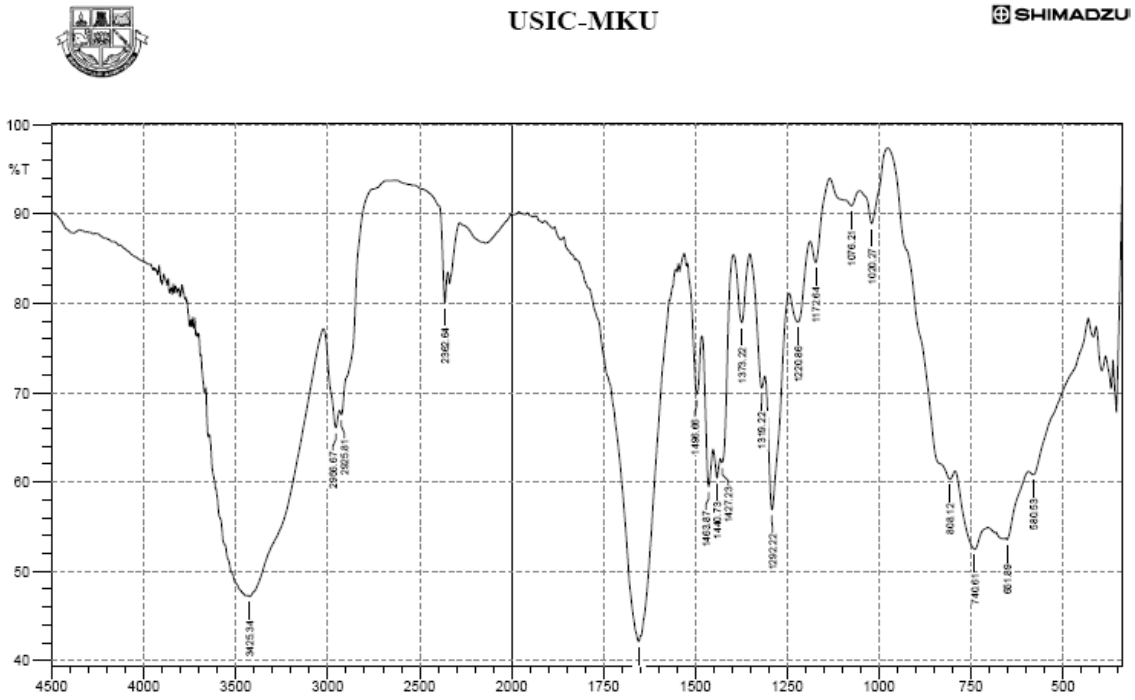
USIC-MKU
SHIMADZU
%T
100
90
80
70
60
50
40
4500
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
3425.34
2926.67
2925.81
2362.64
1496.66
1463.87
1446.73
1427.23
1379.22
1319.22
1292.22
1220.86
1172.64
1076.21
1030.27
808.12
740.61
661.89
580.53

FIGURE – 13D

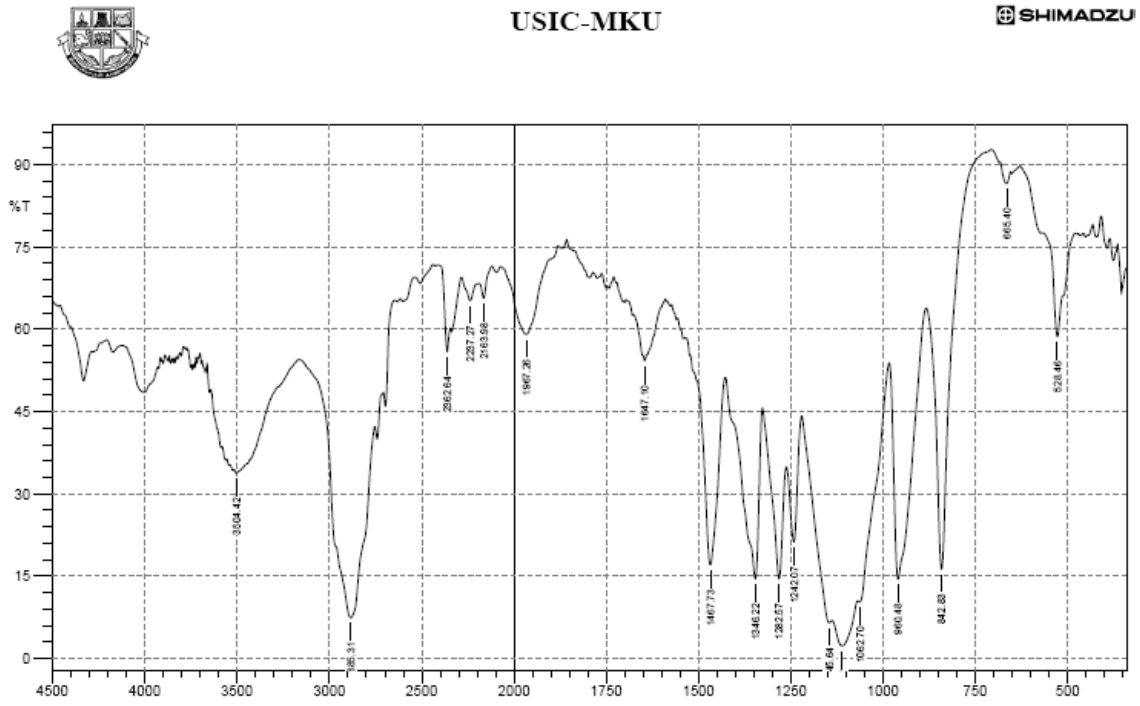
USIC-MKU
SHIMADZU
%T
90
75
60
45
30
15
0
4500
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
3404.42
3185.31
2962.64
2287.22
2163.98
1967.28
1647.10
1467.73
1346.22
1282.57
1242.07
1062.70
960.48
842.83
665.40
628.49

FIGURE – 13E

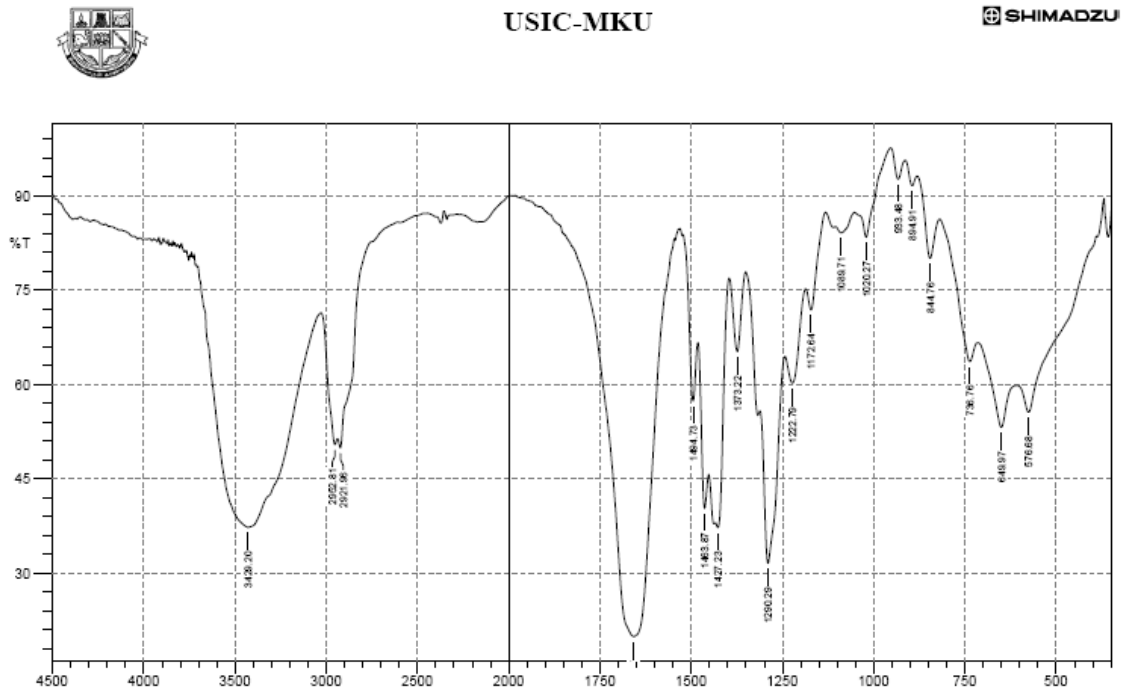
USIC-MKU
SHIMADZU
%T
90
75
60
45
30
4500
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
3426.20
2922.81
2851.06
1464.73
1453.87
1427.23
1373.22
1290.29
1222.76
1172.64
1088.71
1030.27
983.48
894.91
844.76
736.76
649.97
576.68

FIGURE – 13F

USIC-MKU

SHIMADZU

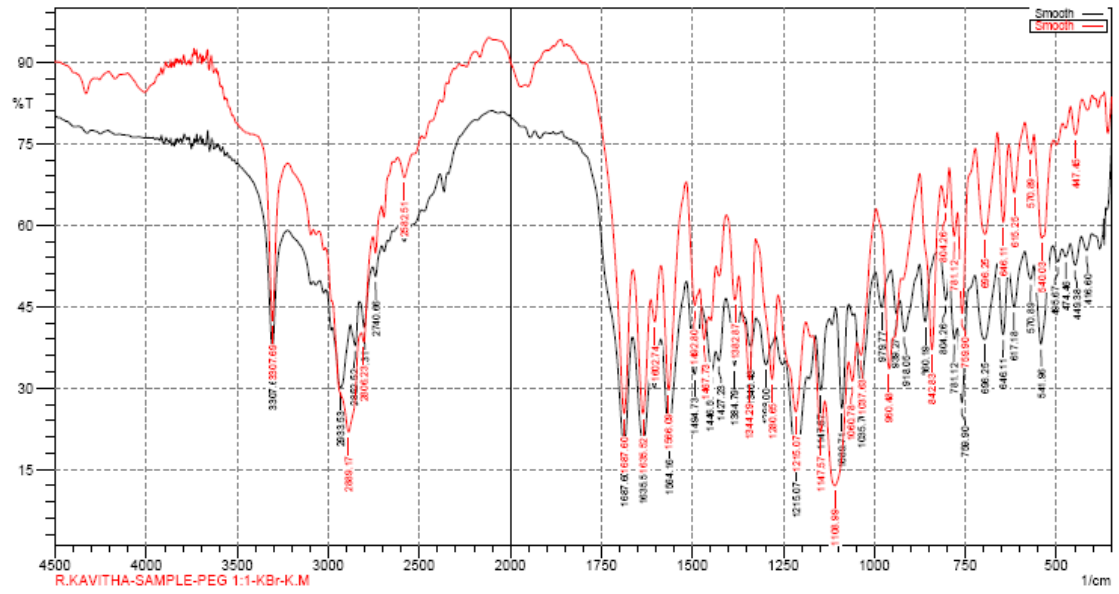

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FIGURE – 13G

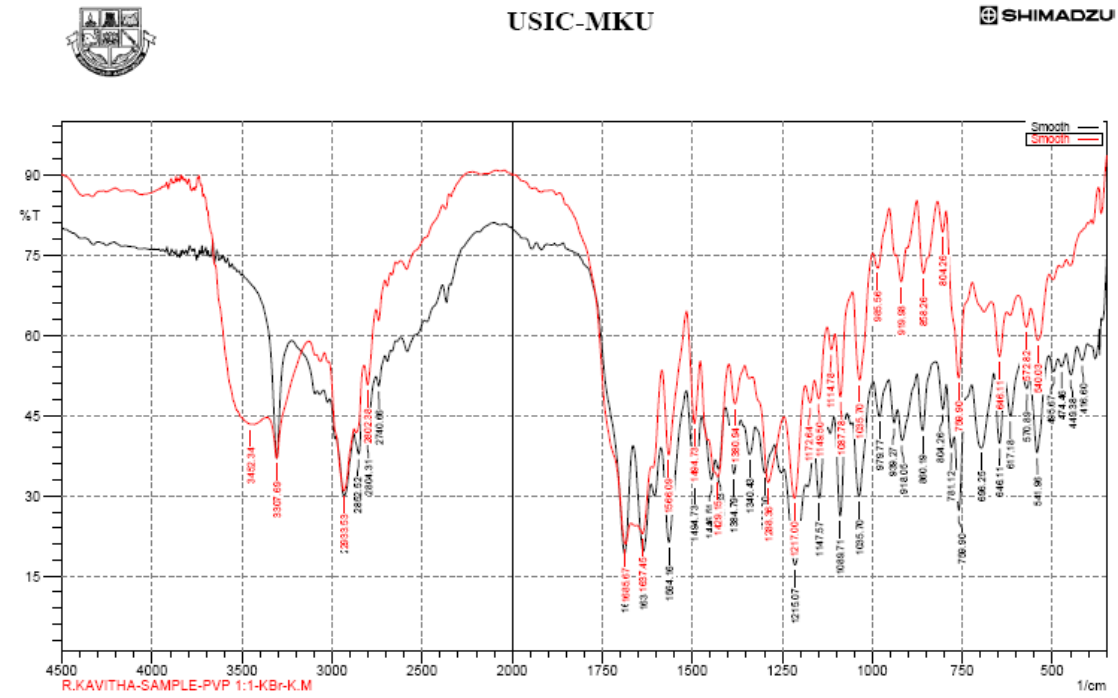
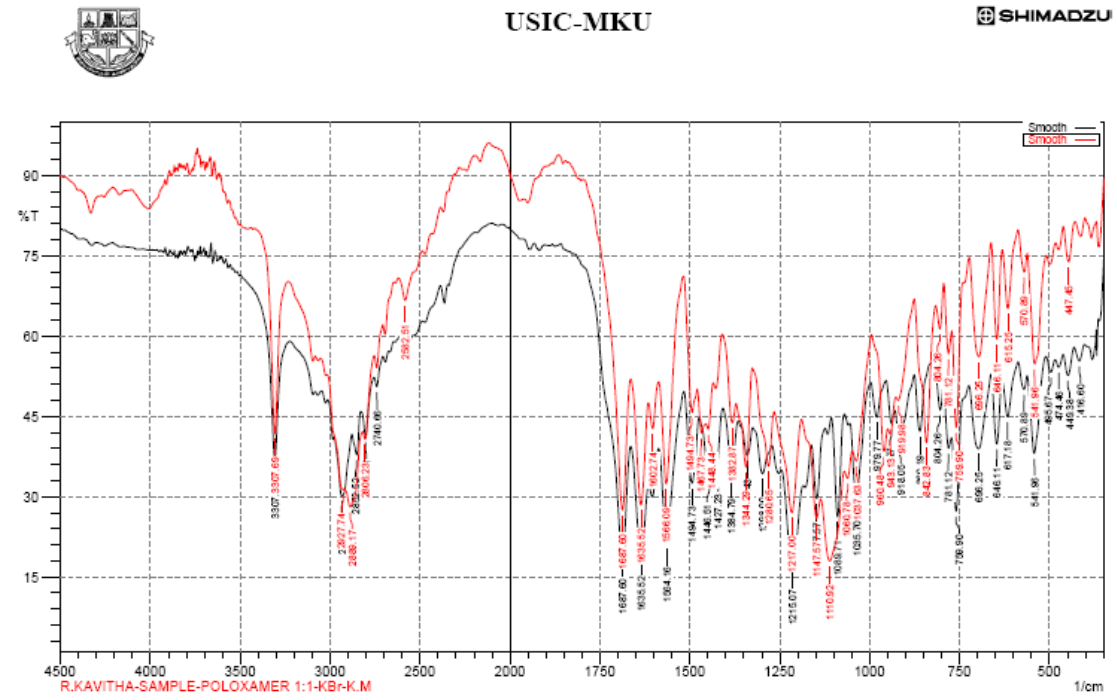

USIC-MKU
SHIMADZU
Smooth
Smooth
%T
90
75
60
45
30
15
4500
4000
3500
3000
2500
2000
1750
1500
1250
1000
750
500
1/cm
R.KAVITHA-SAMPLE-PVP 1:1-KBr-K.M
Comment;
Resolution;
Apodization;
Date/Time; 7/14/2011 5:03:18 PM
User; USIC

FIGURE – 13H



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Apodization;

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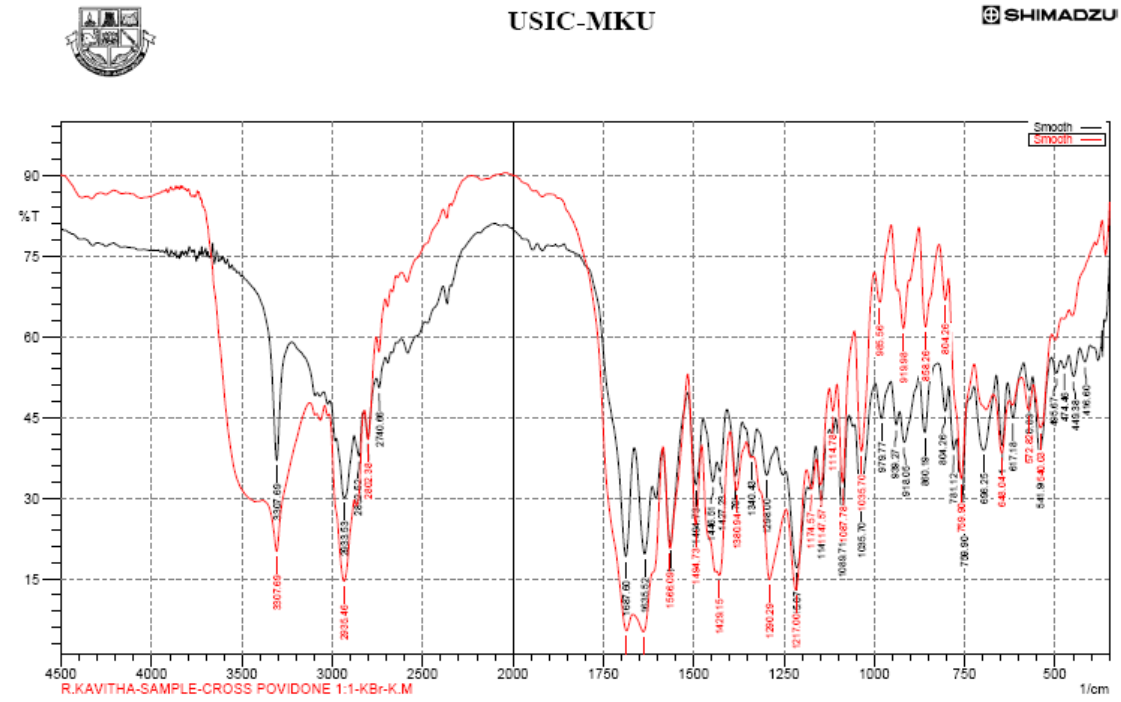
User; USIC

FIGURE – 13I



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